

## "Patient-specific guides for bone tumor surgery. From in-vitro validation to clinical cases"

Paul, Laurent ; Docquier, Pierre-Louis ; Cartiaux, Olivier ; Delloye, Christian ; Banse, Xavier

### Abstract

Objectives: Bone tumor often requires a surgical resection of the tumor. Some tools have been developed to assist the surgeon during the pre-operative and intra-operative steps. The planning leads to accurately define the extension of the tumor, plan resection trajectories (including a safe margin) and select an optimal allograft (if required). The transfer into the operative room has been achieved using a specifically modified navigation system. Since few months, patient-specific devices have come up to guide the saw blade during bone cuttings, such as total knee arthroplasty. This technology has been transposed to resect bone tumors. An experimental study has been led on sawbones to assess the accuracy of the method and compare the results with the one of a previous experiment using conventional and navigated methods. We present the preliminary results of this new experiment and some clinical cases that have already benefited from the technique. Materials a...

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- 13<sup>th</sup> Symposium EMSOS Nurse Group
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# ABSTRACTS

\*S.Mapelli, P.A.Daolio, F.Lazzaro, R.Zorzi, P.Zacconi, S.Bastoni.

^A.Parafioriti, "G.Arborio, °F.Giardina,

\*Orthopaedic Oncology Department; ^ Pathology Department; °Radiology Department.

Gaetano Pini Orthopaedic Institute – Milan – Italy.

°Course of Specialization in Orthopaedics - University of Milan

**Objective:** The number of the patients and the importance of the pelvic lesions that occurred in the Orthopaedic Oncology Unit of the G.Pini Orthopaedic Institute are progressively increased during the last 15 years. Compared to surgical treatment on the extremities, surgery of pelvic malignancies remains challenging. For this reason we decided to revise the data of the complete series of these lesions in order to get indications for the future cases

**Materials and methods:** The pathological and the surgical files of the patients that were registered in the Unit for a pelvic lesion from 1998 to 2011, were revised, compared and analyzed. 258 patients were identified and divided in 3 groups. a)109 patients had only a core or/and a surgical biopsy but did not require a surgical therapy: 69 lesions were malignant, 7 were benign and in 33 cases the lesions were not oncologic or the biopsy was not diagnostic. b)64 patients underwent to a surgical treatment for benign or not neoplastic lesions: the more frequent histotypes were Osteocondroma (15), Osteoid osteoma (9), Osteoblastoma, Simple Cyst and Langherans cell Histiocytosis (6), ABC and GCT (4). c)The others 85 patients received an excision and reconstruction, if needed, for a malignant tumor: the data are reported in the results.

**Results:** In the malignant group there were 54 males and 31 females; the minimum age was 6 years and the maximum 80, with a mean age of 46; the more frequent tumor was the Chondrosarcoma (20 central, 12 peripheral, 2 dedifferentiated) followed by the pPNET/Ewing tumor (14), the Metastasis (12), the Leiomyosarcoma (7), the Osteosarcoma (6), the Angiosarcoma (4) and other types (8). 10 patients had an amputation; 5 had a simple curettage; the resections were classified as: type I (25); type II (8); type III (9); type II+III (11); II+I (7); I+IV (8); I+II+III (1), II+I+IV (1). The margin, evaluated only in the primary lesions, was intralesional in 9 cases, marginal in 15, wide in 39 and radical in 10. The bone reconstruction was not necessary in 27 patients and was not done in 6 (simple *coaptation*); 8 lesions were filled or replaced with PMMA; 3 patients had an hip transposition; 20 hip joint were reconstructed with prosthesis; bone grafts were used in 15 cases (10 auto and 5 allo); 11 patients had soft tissue or capsular reinforcement with mesh, Marlex or Trevira tube. Complications, functional results, recurrences and follow-up are reported in an articulated analysis.

**Conclusions:** In the group of simple biopsies, the relevant number of not oncologic and not diagnostic/not conclusive reports suggest the need to check more accurately the indications for the biopsies but also the importance to follow the patients with the not conclusive reports to avoid a possible delay in the diagnosis of a latent tumor (mainly lymphomas). In the group of malignant lesions there are many types of surgical reconstructions. The experience of the team and their learning curve are decisive in a correct balance of the multiple factors influencing the final surgical solution: histotype and extension of the tumor, prognosis, risk of fracture, age, possible alternative therapies and functional expectations has to be considered. Anyway the complexity and the difficulty of this kind of surgery in the pelvic location justify the high percentage of complications that are to be considered before every decision.

## SURGICAL TREATMENT OF MALIGNANT PELVIC BONE TUMORS INVOLVING THE SACROILIAC JOINT. EXPERIENCE OF SINGLE INSTITUTION

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Sushentsov E., Musaev E., Shipahin S., Valiev A., Nered A., Aliev M.  
N.N.Blokhin Cancer Research Center, Russia, Moscow

**Introduction:** Bone tumors of the sacroiliac joint often have a poor prognosis because of late diagnosis and difficult treatment.

**Purpose:** To assess the surgical technic using for resection and reconstruction of bone tumors involving the sacroiliac joint and estimate their effects on oncological and functional results.

**Materials and methods:** Between 2004 and 2012 years thirteen patients were operated with primary and metastatic bone tumors involving the sacroiliac joint. In study included 7 female and 6 male, age range 19 – 61, mean 39 years. Histology rate was presented with hondrosarcoma – 3 cases, Ewing sarcoma – 3, Metastasis of renal-cell carcinoma – 3, Alveolar sarcoma and Osteosarcoma in one case, respectively. The grading of primary tumors was based on Enneking classification. The functional results was based on the MSTS scoring system. Surgical technic included tumor removing, pelvic ring reconstruction with bone cement and instrumentation and followed by recto-abdominal flap reconstruction. BrainLab navigation system was used for radical resection and instrumentation in two cases.

**Results:** The mean surgical time was 7 hours, bloodloss was 4660 ml. Large resection with adequate margins was in 10 cases, marginal in 2 cases, and contaminated once. The mean follow-up was 35 months, from 3 to 83 months. Two patients with Ewing sarcoma died from metastatic disease, one died from recurrence of disease (with contaminated margin of hondrosarcoma) and one - from renal failure. The deep infection occurred in 3 patients without recto-abdominal flap reconstruction, other patients had good wound healing and early ambulatory. The mean MSTS score was 66,9%.

**Conclusion:** Tumor resection of the sacroiliac joint is difficult surgical procedure with uncertain prognosis. Patient with Ewing sarcoma had poor oncology results. Today gold standard of surgical treatment of this pathology is bone resection with pelvic ring reconstruction and followed by recto-abdominal flap.

G. Bianchi, M. De Paolis, P. Ruggieri, N. Fabbri

<sup>1</sup>Istituto Ortopedico Rizzoli, Bologna, ITALY

**Objectives:** Porous tantalum has been successfully used during the last decade in joint revision surgery associated with severe bone defects. Purpose of this study is to analyse clinical results obtained using modular porous tantalum implants in primary reconstruction after tumor resection or in revision surgery of a pre-existing failed tumor reconstruction of the pelvis and lower extremity.

**Materials and Methods:** It is a retrospective study of 19 patients (8 males, 11 females) who underwent revision surgery for a failed tumor implant (16 cases) of hip-pelvis (10 cases), knee (5 cases) and ankle (1 case), and of 2 primary reconstruction of hip-pelvis after surgical management of bone malignancy (2 cases) or reconstruction of a massive non-oncologic pelvic defect (1 case); average age at the time of surgery was 35 years (22-55 yrs). Cause of failure in revision cases was aseptic loosening (8 cases) or deep infection (9 cases). Revision of infected cases was managed in 2 or more stages. All patients presented severe segmental bone defect as result of primary tumor management and/or recent cause of failure. Bone defect has been managed in all cases with modular porous tantalum implants uncemented at the host bone interface and cemented in contact areas with "augments", always used, in association with morcellised bone grafts to fill residual cavitory defects, and with a megaprosthesis in 9 cases (6 proximal femur, 2 distal femur, 1 proximal tibia). Minimum follow-up in all cases is 2 years, average follow-up is 5 years (2.5-8.5 yrs).

**Results:** One case of refractory infection and one case of recurrent dislocation required further surgery. Porous tantalum implant made revision surgery easier and has shown excellent features also when used for primary pelvic reconstruction. In all cases the porous tantalum implant is well-fixed and functioning at last follow-up. Porous tantalum has provided solid and reliable fixation in challenging biomechanic settings, where it seems to be potentially superior to alternative reconstructive techniques.

**Conclusions:** Porous tantalum clinical performance was very satisfactory at a medium follow-up approaching 5 years and is extremely promising in musculoskeletal oncology as articular and segmental reconstructive technique. Longer follow-up is necessary to identify possibly later failures.

# TREATMENT OF MALIGNANT OR AGGRESSIVE BONE TUMORS OF PELVIC GIRDLE BY MICROWAVE ABLATION

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Qing-Yu Fan, Ma Boan, Zhou Yong, Zhang Minhua, He, Yang Tong Tao, Long Hua, Zheng Lian He, Wang Yu Chai, Li Zhao  
 Department of Orthopedic Surgery, Tangdu Hospital, Fourth Military Medical University, Xi'an, China, 710038  
 Correspondence to: Prof. Qing-Yu Fan  
 (E-mail: bonetm@fmmu.edu.cn)

Tumors in the pelvis not only carry a worse prognosis but their resection and reconstruction are a challenge, even to the most experienced orthopaedic oncologist. ( From **What's New in Musculoskeletal Oncology** Valerae O. Lewis *J Bone Joint Surg Am.* 2009;91:1546-1556. doi:10.2106/JBJS.I.00375)

The current widely used surgical treatment is en bloc resection of tumor-bearing bone followed by reconstruction. The high rate of complication and mechanical instability often contribute to poor results.

**Main Concept & Method** - After careful dissection of the tumor-bearing bone from surrounding normal tissues, the microwave antennae array was inserted into the tumor mass for emitting electromagnetic microwave which produces tumor cellular death via thermo-coagulation. The main concept here is to achieve a safe margin tumor en bloc ablation (assuming that the tumor is localized in the region of diagnosis) using antenna-guided hyperthermia therapy. Form the preliminary animal and model studies, all tissues including the underlying bone and marrow will be completely devitalized (cell death and protein denatured) after heated to 85-120°C for 20 minutes. During surgery, multiple thermocouples were placed in various critical locations to monitor the temperature within and around the tumor bulk. These died tissues were removed and/or curetted leaving behind the defective bone for reconstruction using any of the currently accepted methods, materials and implants including segmental prosthesis. When the lesion is close to the hip joint but not within the joint, this technique could be used with special cooling system to protect the cartilage, thus saving the joint. If the traditionally defined wide margin could be identified using en bloc resection technique, MW ablation can achieve a similar goal while retaining the curetted cortical bone intact, thus making reconstruction easier and more durable.

## Clinic Data:

From May 1994 to December 2009, 204 patients with pelvic malignant or aggressive tumors received radical thermotherapy. (Table 1)

Table 1

Classification	Name	Total number	Gender	Average age
-Tumors with High Malignancy	osteosarcoma/ osteogenic sarcoma	36	Male: 26; Female: 10	24
	Ewing's sarcoma	10	Male: 5; Female: 5	19
	malignant fibrous histiocytoma	7	Male: 3; Female: 4	47
	synoviosarcoma	3	Male: 2; Female: 1	42
	lymphoma	3	All male	18
	leiomyosarcoma	2	All male	33
	myeloma	2	All male	53
	malignant hemangioma	2	All female	42
	malignant neurofibroma	2	Male: 1; Female: 1	38
	mesenchymal sarcoma	1	Female	33
	fibrosarcoma	1	Female	22
	clear cell sarcoma	1	Male	75
	reticular cell sarcoma	1	Male	44
Tumors with Low Malignancy	chondrosarcoma	48	Male: 36; female: 12	38
	chordoblastoma	2	Male: 1; female: 1	44
	osteoblastoma	2	Male: 1; female: 1	50
	hemangio-perithelioma	1	Female	50
	ependymoma	1	Male	50
	synovial chondroma	1	Female	16
	hemangioblastoma	1	Female	32
Aggressive Tumors	giant cell tumor of bone	32	Male: 15; Female: 19	31
	aneurysmal bone cyst	12	Male: 5; Female: 7	22
	Aggressive fibromatosis	3	Male: 2; Female: 1	40
	giant fibroma	3	Male: 2; Female: 1	24
	neurofibroma	1	Male	38
	chondromyxoid fibroma	1	Male	59
Metastatic Tumors	metastatic carcinoma	25	Male: 19; Female: 6	51



The over three-years survival rate for high grade malignancy bone tumor or for low grade malignancy (mainly are chondrosarcoma) is 54.9% and 89% respectively. Almost all aggressive tumor (mainly GCT) got local and system control (only one got amputation). Of 25 patients with isolated pelvic metastatic lesions, 11 patients still lived without evidence of disease for at least three years.

#### Functional results:

1. sixty-five patients who died or lived with disease were excluded from the function analysis. Among the remained 148 patients with high or low malignancy, 127 had excellent hip function, stable, painless, and almost full range of motion although 61 patients have a mild Trendelenberg gait because the gluteus minimus or/and medius had to be sacrificed. They still can be categorized as excellent result according to the standards. Nine patients had good and 12 cases had poor.
2. Complication: Local recurrence occurred in 18 patients (8% local recurred rate), 3 cases had revision surgery and were under following-up, the other nine cases died from lesion. Six patients had deep infection, which resolved by irrigation, debridement, and administration of system antibiotics. A fistula developed in two patients. One had lumbosacral trunk damaged during heating due to that the nerve could not be separated from the tumor. Two patients sustained sciatic notch fractures, which healed in a non-anatomic position. Four patients had hip joint degeneration change.

In the majority of the patients, functional and cosmetic acceptable limbs were reserved.

#### Overall Advantages –

- 1 Greatly simplified the surgery process. Making reconstructive procedure more conservative and less costly.
- 2 Increased the local and system control rate.
- 3 Greatly improved the functional outcome because it could keep the leg length and stability of pelvic girdle.

#### A typical case

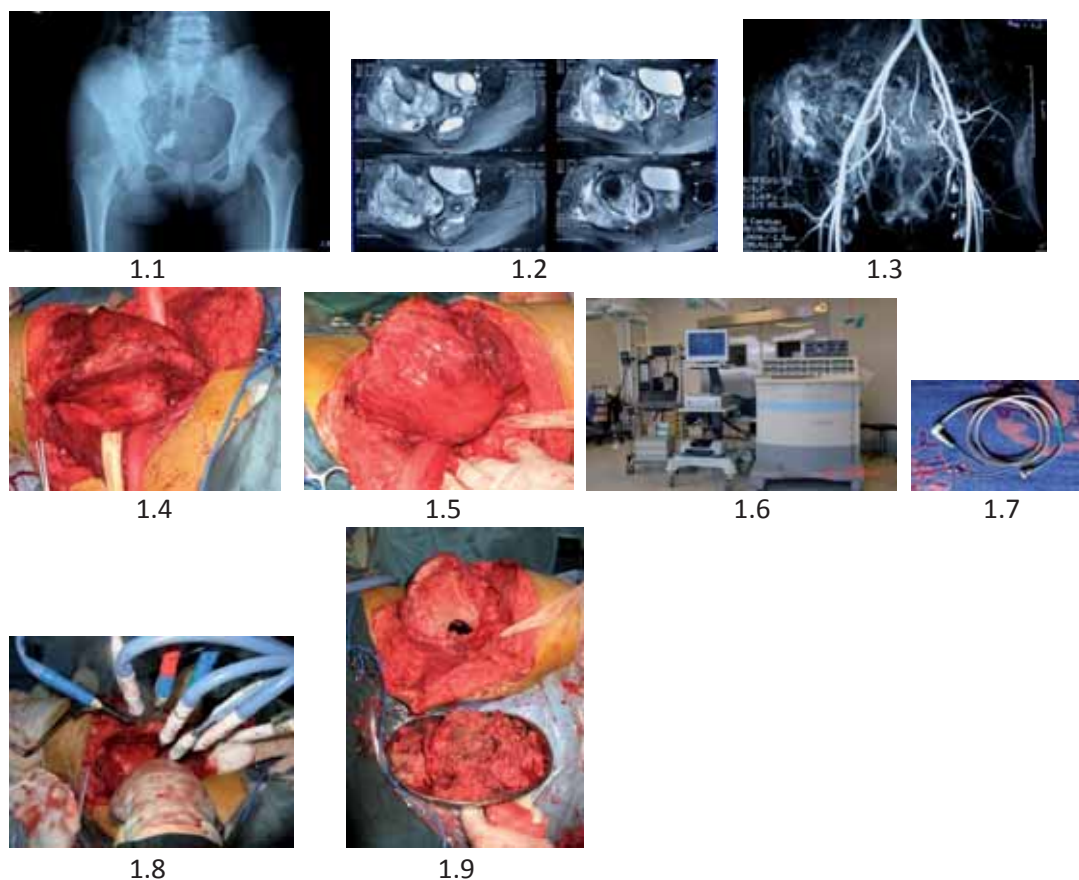


Fig 1: Chandrosarcoma of pelvis.

1.1—1.3: image data shows the great sciatic foramen was filled fully with tumor.

1.4—1.5: intra- and extra-pelvic were explored.

1.6: microwave generator(made by Sea.. company, Nanjing, China)

1.7: antenna

1.8: microwave ablation was carried out.

1.9: remove the devitalized soft tissues. Pelvic skeletal structure was kept perfect with sufficient strength.

## COMPUTER ASSISTED SURGERY FOR PELVIC TUMOURS : LESSONS LEARNT FROM THE FIRST 25 CASES

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Lee Jeys, Rob Grimer

Royal Orthopaedic Hospital, Birmingham, UK

**Objectives:** The pelvis and sacrum remain one of the most challenging locations for surgery in Orthopaedic Oncology. The complex 3D structure, proximity of vital structures, consistency of the tumour and variable position of the patient during surgery. Previous studies have shown that the probability of experienced surgeons achieving a 1cm margin in all 3 planes on a simulated tumour model of the pelvis was less than 50%. Our previously presented series prior to the use of navigation showed that our intralesional rate for pelvic bone tumours was 29% and our long term local recurrence rate was 26%. The aim of the study was to report the experience of the first 25 cases of computer navigation for tumours of the pelvis and sacrum.

**Methods:** From April 2010 to date we have conducted 25 cases of resection of bone tumours of the pelvis and sacrum using the Stryker Orthomap Navigation system, which uses technology to fuse MRI & CT scan, to accurately create a model of the tumour and normal anatomy. At surgery the patient model is correlated with the patients anatomy allowing accurate resection of the tumour. Patients were identified from the database, their demographics and outcomes were analysed.

**Results:** Resection of malignant tumours have been undertaken in 25 patients. These were for 16 primary malignant bone tumours (8 chondrosarcomas, 4 chordomas, 3 osteosarcomas and 1 Ewings sarcoma) and 9 metastases (4 primary rectal tumours with direct invasion into the sacrum, 3 periacetabular breast metastases and 2 solitary renal metastases). In all 22 cases where a clear surgical margin was intended (some initial case in series the navigation was used for implant positioning) then the mean registration error was less than 1mm and the bony resection margins were wide by greater than 5mm. In 2 cases there was tumour contamination (one case a cystic chondrosarcoma ruptured on removal of specimen from the pelvis after resection, and in one case there was a positive soft tissue medial margin on a chordomas where the peritoneum was adherent to the tumour and it torn on tumour removal after resection). There have been no cases of locally recurrent disease to date. The technique allowed more complex resection and reconstruction than would have been possible previously, avoided a hindquarter amputation in 3 cases, saved nerve roots in 4 patients which would have led to incontinence and allowed resection of the primary rectal carcinoma in 4 cases, which would have previously been deemed inoperable.

**Conclusions:** The authors feel this technique has particular merit for use in pelvic surgery and has significantly reduced our intralesional resection rate and allowed more complex surgery and reconstruction.

Andrea Angelini, MD; Roberto Casadei, MD; Elisa Pala, MD; Gabriele Drago, MD; Matteo Romantini, MD; Pietro Ruggieri, MD, PhD

IV Department of Orthopaedics, University of Bologna, Istituto Ortopedico Rizzoli, Bologna, Italy

**Objectives:** Surgical treatment of pelvic tumors with or without acetabular involvement is challenging. Primary goals of surgery include local control and maintenance of good quality of life. Purpose of this study was to evaluate the incidence and outcome of infection after limb salvage surgical resection with or without reconstruction for pelvic bone tumors.

**Material and Methods:** From 1975 to 2010, 274 patients (162 males-112 females) with pelvic bone tumors were treated by surgical resection. Mean follow-up was 7.1 years (range 1-32). Chondrosarcoma (161), Ewing's sarcoma (82) and osteosarcoma (47) were the most common histotypes. According to Enneking's classification, 66 patients had type I (ilium), 24 type II (periacetabular) and 25 type III (anterior arch) pelvic resection. Combined resections were performed in 42 cases (type I-II), 79 cases (type II-III), 25 cases (type I-II-III) and 13 cases (type I-IV). In 139 cases reconstruction was performed, in 135 there was no reconstruction. Special attention was given to the assessment of deep infections, their treatment and outcome.

**Results:** Deep infections were observed in 54 cases (19.7%) at mean follow-up of 11 months. There were 19 infections in 135 cases without reconstruction (14%) and 35 over 139 with reconstruction (25%). In 33 patients (61%) infection occurred within 4 weeks postoperatively, in 12 within 6 months and in 10 after 6 months. Most frequent bacteria causing infection were *Stafilococcus* species (40%), *Enterococcus* and *Escherichia Coli* (31%), *Pseudomonas Aeruginosa* (9%). Actuarial survival to infection was 88%, 83% and 79% at one month, one and ten years respectively. Surgical treatment consisted in one (37%) or more (26%) surgical debridements, combined with antibiotics therapy according to coltures. In 16 cases the implant was removed, while 5 cases (9.3%) had an external hemipelvectomy (one due to both persistent infection and local recurrence). The incidence of infection in patients with reconstruction was statistically higher than in patients without reconstruction ( $p < 0.01$ ). No statistical difference was found between periacetabular resections and others. Average MSTS score after treatment of infection was 68.3%.

**Conclusions:** Favourable oncologic and functional outcome can be achieved in selected patients with pelvic bone tumors. Complication rates are high. Reconstruction after resection is related with risk of infection.

## EVALUATION OF THE EFFECTIVENESS OF TREATMENT FOR CHILDREN AND ADOLESCENTS WITH EWING'S SARCOMA FAMILY TUMOR OF PELVIS

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Nisichenko O.A., Shvarova A.V., Glekov I.V., Hestanov D.B., Musaev E.R., Ivanova N.M.

Institute of Paediatric Oncology and Hematology N. N. Blokhin Cancer Research Center, Moscow, Russian Federation

**Aim:** The aim of this study was to evaluate and compare the effectiveness of the treatment of various treatment protocols for children and adolescents with Ewing's Sarcoma Family Tumor of pelvis.

**Materials and methods:** Ninety patients with ESFT of the pelvis were treated at Institute of Paediatric Oncology and Hematology between 1972 and 2007. Three different protocols of chemotherapy were used. Between 1972 to 1988 protocol consisted of VAC for control group (CG) I: 32 pts, nonmetastatic - 25, disseminated -7, between 1988 to 1997 of VACP for control group II: 30 pts, nonmetastatic - 23, disseminated -7. From 1997 till 2007 induction chemotherapy (CT) for pts (28, nonmetastatic - 18, disseminated -10) of investigation group (IG) III consisted of vincristine 1,5 mg/m<sup>2</sup>/d, days 1,8,15, adriamycin 37,5 mg/m<sup>2</sup>/d, days 1,2 as a 24-h infusion, cyclophosphamide 2,1 gr/m<sup>2</sup>/d, days 1,2 (1, 3, 5 cycles), and ifosfamide 2,4 gr/m<sup>2</sup>/d, days 1 through 5, etoposide 100 mg/m<sup>2</sup>/d, days 1 through 5 (2, 4 cycles). Local treatment consisted of radiotherapy in all cases. After local treatment pts of IG received HD CT with melphalan 140 mg/m<sup>2</sup>, busulfan 16 mg/kg. PBCS were reinfused mean 6,0 x10<sup>6</sup> CD34<sup>+</sup>/kg.

**Results:** The 5- year disease-free survival rates were 3,1% for CG I; 13,3% for CG II and 69,8% for IG III. These results are significantly worse for CG I and II than the ones achieved in 28 patients of IG III with new innovative methods for the treatment.

Only one patient had surgical treatment in the amount of resection of the ischium and pubic bone defect with endoprosthesis reconstruction of the pelvis and hip replacement.

**Conclusion:** The use of an innovative program of intensive therapy significantly improved clinical outcomes and increase the 5-year disease-free survival in 28 patients of Group III to 69.8%.

Stefano Ferrari<sup>1</sup>, Emanuela Palmerini<sup>1</sup>, Nicola Fabbri<sup>2</sup>, Eric Staals<sup>2</sup>, Cristina Ferrari<sup>1</sup>, Emanuela Marchesi<sup>1</sup>, Pietro Rugieri<sup>2</sup> Marco Alberghini<sup>3</sup>, Piero Picci<sup>1</sup>

<sup>1</sup>Oncology Department, Rizzoli Institute, Bologna, Italy

<sup>2</sup>Surgical Oncology Department, Rizzoli Institute, Bologna, Italy

<sup>3</sup> Surgical Pathology Department, Rizzoli Institute, Bologna, Italy

**Background:** Information is scarce on treatment of pelvic osteosarcoma (POS) as most study protocols for osteosarcoma include patients with extremity tumors and aged up to 30-40 years.

Patients younger than 41 years with high grade POS were enrolled in a monoinstitutional prospective study. Whenever possible patients were surgically treated. The systemic treatment was given according to two chemotherapy protocols consisting of methotrexate, cisplatin, doxorubicin (MAP) and standard dose (SD) or high-dose (HD) ifosfamide (IFO).

**Results:** Forty patients (9 with synchronous lung metastases) ranging between 11 and 36 years (median age 22 years), with POS were included. The most frequent histological subtype was the osteoblastic one followed by the chondroblastic histotype that was observed in 37.5% of patients. Complete surgical remission (CSR) was achieved in 65% of the patients. Chemotherapy: 18 patients had MAP/SDIFO, 22 MAP/HDIFO. Primary chemotherapy was given to 25 patients and 6 (24%) of them had a good histological response. Median follow-up was 32 months (4-134), 5-year overall survival (S) was 27.5%: 33% in localized and 0 in metastatic patients ( $p=0.02$ ); 45% in patients with CSR and 0 for no CSR ( $p=0.001$ ). Local recurrence rate was 46%. In patients with CSR, 5-year probability of S was 32% with MAP/SDIFO regimen and 59% with MAP/HDIFO regimen ( $p = 0.3$ ).

**Conclusions:** Local control is the major issue in treatment of pelvic osteosarcoma. Poor pathological response and the high incidence of chondroblastic variant indicate different biological characteristics between pelvic and extremity osteosarcoma. A chemotherapy treatment with MAP and high-dose ifosfamide might be beneficial patients with pelvic osteosarcoma and warrant further investigation .



# OUTCOME ASSESSMENT OF HIGH GRADE CHONDROSARCOMA EXPERIENCES FROM THE VIENNA BONE AND SOFT TISSUE REGISTRY

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Philipp T. Funovics, Martin Dominkus, Joannis Panotopoulos, Susanna Lang, Reinhard Windhager  
Medical University of Vienna Department of Orthopaedics, Vienna, Austria

**Background:** Chondrosarcoma is the second most common primary bone tumor, yet a rare entity, and the identification of prognostic factors is still regarded a difficult challenge. Aim of this study was to retrospectively present a single institution experience with high grade chondrosarcoma over a forty year time span.

**Methods:** Between January 1972 and December 2011, a total of 175 patients have been treated for high grade chondrosarcoma at the Medical University of Vienna Department of Orthopaedics. Low-grade lesions and tumors of the small bones have been included from this investigation. The cohort included 102 males (58%) and 73 females (42%) with an average age of 52 years (range, 16 to 87; median, 54). Mean follow-up was 67 months (range, 1 to 412; median, 44). Ninety-five tumors were located in the trunk (54%), including 62 pelvic lesions (35%) and 80 tumors arose in the extremities (46%) with the femur being the most predominant site (46 lesions; 26%). Eleven tumors were regarded as extraskeletal chondrosarcoma (6%), and 18 patients presented with primary metastatic disease (10%). Eight tumors (5%) were regarded irresectable and conveyed to conservative treatment, 167 patients (95%) underwent surgery including endoprosthetic reconstruction in 68 (39%) and initial amputation in 24 (14%).

**Results:** Eighty-seven patients (50%) died throughout follow-up. Median overall survival of all patients was 80 months with a five- and ten-year survival rate of 56% and 45%, respectively. Age ( $p<0.001$ ), female gender ( $p=0.013$ ), tumor site in the trunk ( $p=0.003$ ) and primary metastatic disease ( $p=0.008$ ) were strong negative predictors of outcome. Local recurrence was observed in 19 of 167 operated patients (11%). Local recurrences occurred up to 117 months postoperatively with a five- and ten-year local recurrence-free survival rate of 83% and 81%, respectively. Women showed a better local recurrence-free survival ( $p=0.046$ ). Metastases were observed in 33 cases (19%). Correspondingly, the five- and ten-year metastasis-free survival rate was 75% and 71%, respectively, with a trend towards worse outcome of soft tissue chondrosarcoma ( $p=0.053$ ). In multivariate analysis age ( $HR=1.04$ ), site ( $HR$  for extremity=0.42) and primary metastatic disease ( $HR=2.59$ ) were statistically significant predictors for overall survival.

**Conclusion:** High grade chondrosarcoma is an aggressive entity, especially outcomes of truncal tumors can be limited by the inability to achieve surgically adequate margins, leading to a considerable rate of local recurrence. Also, the unfavourable outcome for patients with metastatic disease underlines the need for further adjuvant therapies.

# RADIOFREQUENCY ABLATION OF LOWGRADE CHONDROSARCOMAS: EFFICACY AND INITIAL EXPERIENCES OF A NOVEL TECHNIQUE IN PRIMARY BONE TUMOUR SURGERY.

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Dierselhuis EF<sup>1</sup>, vd Eerden PJM<sup>2</sup>, Hoekstra HJ<sup>3</sup>, Bulstra SK<sup>1</sup>, Suurmeijer AJH<sup>4</sup>, Jutte PC<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, University Medical Center Groningen, University of Groningen, the Netherlands

<sup>2</sup>Department of Radiology, University Medical Center Groningen, University of Groningen, the Netherlands

<sup>3</sup>Department of Surgical Oncology, University Medical Center Groningen, University of Groningen, the Netherlands

<sup>4</sup>Department of Pathology, University Medical Center Groningen, University of Groningen, the Netherlands

**Introduction:** To date, central chondrosarcoma (CS) grade I within the long bones is treated either by resection or curettage with local adjuvant. Recent reports suggest that local treatment is sufficient in most cases, with better functional outcome as a result. Given the fact that CS grade I typically has a very mild biological behaviour, we hypothesized that minimal invasive treatment would be the next step using radiofrequency ablation (RFA). The purpose of the study is to demonstrate an effective ablation of central CS grade I tumour cells in the long bones using RFA.

**Patients and methods:** A prospective study was designed to evaluate the tumour kill efficacy of RFA in central CS grade I. A total number of 20 patients were treated by CT guided RFA. Three months later, patients received usual care by curettage with phenol/ethanol and bone cement as local adjuvant. Material retrieved during curettage was sent for histopathological analysis to assess the percentage of tumour necrosis as primary endpoint. In addition, patient and tumour characteristics were documented. MSTS scores were noted 6 and 12 weeks after RFA and curettage. In 10 patients, MSTS scores after one year were also calculated.

## **Results:**

### Primary endpoint

In 9 patients, 100 percent necrotic tissue was found in material obtained during curettage (R0). In 5 other patients, the amount of non viable cells was estimated 95-99% (R1). In 6 patients, the percentage of necrosis was <95% (R2). Of all tumours localised in the diaphysis (n=6), 5 (83%) were completely destructed, compared to 4/14 (29%) in the epimetaphysis (p=0.02). Of all tumours ablated > 30 mm, only 5/11 (45.5%) were R0 or R1, compared tot 9/9 (100%) in tumours <30 mm (p=0.006).

### Secondary endpoints

All patients with a tumour in the lower extremity (n=16) had a 50% weight-bearing regime for the first six weeks, increased to 100% after three months. Mean MSTS scores 6 weeks after RFA were 27.1 (23-30) compared to 18.1 (12-25) 6 weeks after curettage (p<0.001). 12 weeks after RFA, MSTS scores were 27.2 (23-30) versus 22.9 (15-30) 12 weeks after curettage respectively (p<0.001). One year after curettage, scores averaged 27.4 (24-30). No adverse events were seen after RFA. In two patients, a pathological fracture occurred after curettage. All patients were discharged from the hospital several hours after the RFA procedure. For curettage, patients were admitted three to five days.

**Conclusions:** In conclusion, we have demonstrated that RFA is capable of complete eradication of small grade I CS in the long bones. Hereby, minimal invasive surgery can be used as an alternative in the treatment of these tumours. It can be safely performed in day-care, with a very quick return to daily activity. For the long term, it has to be proven that oncological outcome will be as satisfying. Currently, size of tumour and localisation within the bone are the main predictors of success, with varying efficacy rates. Therefore, more consistency is needed and further research is being done at present to improve accuracy of the ablation procedure.

## PELVIC CHONDROSARCOMAS: REVIEW OF THE ISTITUTO RIZZOLI EXPERIENCE

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Pietro Ruggieri, MD, PhD; Andrea Angelini, MD; Nicola Fabbri, MD; Andreas F. Mavrogenis, MD; Gabriele Drago, MD; Carlo Romagnoli, MD; Marco Manfrini, MD.

IV Department of Orthopaedics, University of Bologna, Istituto Ortopedico Rizzoli, Bologna, Italy

**Objectives:** Aim of this retrospective study was to review the long-term oncologic and functional outcome of surgical management in a large series of patients with pelvic chondrosarcomas (CS) treated at a single institution.

**Material and Methods:** We analyzed 235 patients treated at our institution between 1975 and 2008: 144 males (61%) and 91 females (39%) with a mean age of 46.6 years (range, 15 to 81 years). There were 101 central CSs (16, 66 and 19 cases grade 1, 2 and 3 respectively), 83 peripheral CSs (42, 40 and 1 cases grade 1, 2 and 3 respectively), 33 dedifferentiated CSs, 4 clear cell CSs, 2 mesenchymal CSs and 2 periosteal CSs, while in 10 cases it was not possible to define the histologic variant. Tumor involved the iliac wings in 57 cases, iliac wing and sacro-iliac joint in 8 cases, iliac wing and periacetabular bone in 34 cases, anterior arch and periacetabulum in 49 cases, anterior arch only in 22 cases and the entire hemi-pelvis in 33. Forty-one patients had an external hemipelvectomy (17%), whereas 194 patients (83%) underwent a limb-salvage procedure: 105 resections without reconstruction and 89 resections with reconstruction. Margins were wide in 151 cases, wide but contaminated in 30 cases, marginal in 41 cases and intralesional in 13 cases (in 7 of these cases a debulking procedure was performed due to extension of the tumor).

**Results:** The overall survival evaluated with Kaplan Meier curve was 82%, 73% and 70% at 5, 10 and 15 years respectively. At a mean follow up of 9 years (2–32 years), 158 patients (68%) were continuously disease free, 13 were alive without evidence of disease after treatment of local recurrence, 49 patients (21%) died of their disease, 12 patients (5%) died of other causes and 16 patients (6.8%) alive with disease. Incidence of local recurrence was 29.8% (70 patients) and survival to local recurrence was 74%, 68% and 65% at 5, 10 and 15 years respectively. Incidence of LR was statistically higher in surgery involving periacetabular areas than iliac wing ( $p=0.0372$ ) or anterior arch ( $p=0.0137$ ). In central and peripheral CSs, high-grade tumors correlated with worse survival ( $p=0.012$ ). There was no statistical difference in survival between peripheral and central CSs ( $p=0.0763$ ), while comparing both central CSs and peripheral CSs with dedifferentiated CS, this latter had a significantly worst prognosis ( $p<0.0001$ ).

**Conclusions:** Surgery is the mainstay of treatment for pelvic CS. External hemipelvectomy is reserved to cases where it is not otherwise possible to achieve adequate margins. Pelvic location, especially the acetabulum, offers challenging technical problems to reliable and lasting reconstruction. There is a significant correlation between tumor grading and survival. The lack of adjuvant suitable chemotherapeutic agents leads to a worsening of prognosis at long-term.

*Domenico A. Campanacci, Massimiliano Ippolito, Filippo Frenos, Giuseppe Caff, Giovanni Beltrami, Guido Scoccianti, Rodolfo Capanna*

*Department of Orthopaedic Oncology, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy*

**Objectives:** The pelvis and proximal femur are the most frequent sites of occurrence of chondrosarcoma (CS) of bone, and axial CS were seen to behave more aggressively than appendicular skeleton lesions. Currently, surgical excision remains the elective treatment option for pelvic chondrosarcoma due to its scarce response to chemotherapy and radiationtherapy. The purpose of the present study was to review the patients treated for a chondrosarcoma of the pelvis at authors' Institution and to identify the risk factors for local and systemic control of the disease.

**Materials and Methods:** Fortytwo patients with diagnosis of pelvic CS, treated at author's Institution between 1994 to 2011, were included in the study. They were 26 males and 16 females with a median age of 50 years (min 15 - max 75). The diagnosis was central CS (CCS) in 34 cases and peripheral CS (PCS) in 8 cases. In 2 cases, the CCS was a local recurrence after a previous surgical treatment. The hystological grading of 34 CCS was: G1 in 4 cases, G2 in 20, G3 in 4 and G4 (dedifferentiated) in 6 cases. The hystological grading of 8 PCS was: G1 in 6 cases, G2 in 2 cases. The tumor localization was the iliac wing in 7 cases (Type I resection), the anterior pelvic arch in 6 (Type III), the acetabular area in 26 (Type II in 6; Type I-II or II-III in 13; Type I-I-II in 7) and the sacroiliac joint in 3 cases (Type I-IV). The surgical treatment of 34 CCS was resection in 24 cases, intralesional curettage in 3 cases and hemipelvectomy in 7 cases. Surgical margins after CCS excision resulted radical in 4 cases, wide in 19, marginal in 8 and intralesional in 3 cases (intentional intralesional curettage). The surgical treatment of 8 PCS was conservative resection in all cases. Surgical margins after PCS excision resulted wide in 6 and marginal in 2 cases. After conservative resection of the tumor (35 patients), no reconstruction was performed in 17 cases while a massive allograft with THA was used in 15 cases, an ischiofemoral arthrodesis in 1, a saddle prosthesis in 1 and a hip rotationplasty in 1 case.

**Results:** At a median follow up of 52 months (min 2- max 209), 25 patients were continuously disease free (59.5%), 3 patients were alive with disease, 12 patients had died of disease and 2 patients had died of another cause. A local recurrence was observed in 11 patients (26%), 9 in CCS and 2 in PCS. Local recurrence was observed after conservative resection in 8 cases and after hemipelvectomy in 3 cases. Pulmonary metastases occurred in 13 patients (30.9%), 11 in CCS and 2 in PCS. Local recurrence free survival was 64.1% at 5, and 15 years and overall survival was 62.9% and 47.1% respectively at 5 and 15 years. A statistically significative correlation was found between local recurrence and type of resection showing the tumor location in the sacroiliac joint (Type I/IV resection) a risk factor for local control of the disease. Histological grading resulted a statistically significant risk factor for survival.

**Conclusions:** The review of our experience on pelvic CS confirmed their worse prognosis on respect to appendicular skeleton localizations. In 62% of cases the tumor involved the acetabular area. CCS were most frequently G2 (59%) and PCS were most frequently G1 (75%). Limb salvage rate in our series of pelvic CS was 83.3%. In three G1 CCS, an intralesional curettage was performed (grading was confirmed at final histologic examination) and no local recurrence was observed so far (average 64 months, min 38-max 99). In the remaining 39 patients, adequate surgical margins were achieved in 74% of cases. Statistical analysis showed a correlation between local recurrence and tumor location (higher risk in the sacroiliac area) and between patients' survival and tumoral histologic grading.

# MEGAPROSTHETIC RECONSTRUCTION FOR CHONDROSARCOMA OF THE EXTREMITIES: EVALUATION OF THE FUNCTIONAL AND ONCOLOGICAL OUTCOME

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Markus Nottrott, Marcel Henrichs, Georg Gosheger, Jendrik Harges, Arne Streitbürger

Department of Orthopaedics, University Hospital Münster, Münster, Germany

**Objectives:** The treatment of Chondrosarcoma of bone is still challenging. Surgery keeps the only effective treatment option, while still missing adjuvant therapies. The wide tumour resection according to Enneking is the treatment of choice in high- and intermediate-grade chondrosarcoma. Only for low-grade chondrosarcoma of the long bones conservative surgery is feasible for special indications. The use of megaprosthesis for defect reconstruction is superior to allograft or biological reconstructions, however, despite aggressive surgery high rates of local recurrences and metastasis are common. Further, infection still remains a severe implant related complication.

**Material and Methods:** Between 1992 and 2006 we used megaprotheses in 78 patients (32 women, 46 men) with the diagnosis of chondrosarcoma of the limb. Of these, eight were treated initially for the primary tumour at another institution, of whom all were treated intralesionally. Most frequent tumour site was the distal femur (n=24) and the proximal femur (n=24) followed by the proximal humerus (n=21).

Mean age at primary diagnosis was 55.2 years. Tumour grading was grade I (GI) in 17 patients, GII in 42, GIII in 7, and de-differentiated (DD) chondrosarcoma in 12 patients.

**Results:** Median follow-up was 62 months with a minimal follow up of 20 months or until death. Overall survival was significantly linked to the tumour grade. 21 patients died of disease (G II 19.0%, G III 28.5%, DD 91.7%) after a medium of 24 months. In 91% wide resection margins were achieved. Local recurrence rate was 7.6% for all tumours but even higher (41.7%) for high-grade chondrosarcoma. Local recurrence was not linked to the achieved margin. Primary metastases were found in five patients and 26% developed metastases within the follow-up. Although there was no influence of the resection margins on development of metastatic disease. Adjuvant therapy was given to 13 patients however, there was no effect on the overall prognosis (one alive).

Functional results were good in most of the patients. The main prosthesis related complication was infection in 4 cases followed by aseptic loosening (n=3). 11.5% of the patients required surgical revision due to implant related complications and 23.1% due to oncological complications. Secondary amputation was necessary in eight patients because of oncological complications and one due to infection. Prosthetic survival at the latest follow up was 77.3% for the primary implant.

**Conclusions:** The endoprosthetic replacement of chondrosarcoma of the limb provides good functional outcome with low rates of implant related complication and a long prosthetic survival.

However, in absence of effective adjuvant therapies, even the wide tumour resection results in high rates of local recurrences and metastatic disease in high grade chondrosarcoma compared to other primary bone sarcoma.

This is certainly founded in tumour biology and shows that additional adjuvant treatment options are needed.



P. Picci, A. van Maldegem, E. Palmerini, P.D.S. Dijkstra, M. Alberghini, J.V.M.G. Bovee, P. Ruggieri, C. Ferrari, S. Ferrari, H. Gelderblom

Istituto Ortopedico Rizzoli, Bologna, Italy and Leiden University Medical Center, The Netherlands

**Objectives:** Little is known about the survival of central chondrosarcoma when surgical removal of local or metastatic disease is considered unfeasible. Particularly no information is available on survival in this condition. Furthermore this histology is considered chemoresistant and no treatment has been shown effective for these patients (pts).

**Materials and Methods:** To answer this question, pts with non-resectable ("inoperable") central chondrosarcoma from two major European Centers (Rizzoli Institute in Bologna, and Leiden University Medical Center) were pooled for investigation. 171 pts were considered inoperable: 49 cases at first presentation, 122 cases after one or more relapses.

**Results:** The time to development of inoperable disease for the 122 pts who relapsed ranged from 1 to 233 months from first treatment, with a median of 23.5 months.

The site of the inoperable disease was local only in 45 cases, lung only in 72 cases, lung plus local in 39 cases, and also with visceral involvement in 15 cases.

The overall survival for all 171 pts was 48% at 1 year, 24% at 2 years, 12% at 3 years, 6% at 4 years, and 2% at 5 years. The median time to death was 11 months with a range of 1-106 months. In patients with local only unresectable disease, survival was 26% at 36 months (median 18, range 1-104) compared to 7% (median 11, range 1-51) and 8% (median 9, range 1-106) respectively for those presenting with lung disease only or lung plus local disease. In pts with visceral disease median survival was 7 months (range 2-24). The difference between pts with local disease only and the other patterns is highly statistically significant with a p value of 0.0014. Regarding the role of other treatments, 37 pts received systemic antitumour treatment, with a survival of 26% at 36 months, compared to 8% for those pts who did not receive it. Radiotherapy was given in 36 pts and their survival was 27% at 36 months vs 8% for those who did not receive it. Evaluation of the effect of these non-surgical treatments will require further investigations.

**Conclusions:** This pooled analysis of the largest series of inoperable chondrosarcoma pts allowed us to gain insight in the prognosis of these pts, that can serve as benchmark for future studies.

## CHEMOTHERAPY IN CHONDROSARCOMAS. RECENT EXPERIENCE OF N.N. BLOKHIN CANCER CENTER

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Gennady Machak, Igor Chernov, Teimuraz Kharatishvili

**Purpose:** To evaluate the effectiveness of recent chemotherapy regimens in the treatment of patients with chondrosarcoma.

**Patients and methods:** Since 1997, 36 patients received chemotherapy for primary (19) or recurrent/metastatic (17) chondrosarcoma. In primary tumors chemotherapy consisted in combination of doxorubicin (DOX) 60-90 mg/m<sup>2</sup> and cis-platinum (CDDP) 100-120 mg/m<sup>2</sup> (11) administrated IV or IA. Last years ifosfamide (IFO) containing regimens (IFO 6 g/m<sup>2</sup>+DOX 60 mg/m<sup>2</sup>+CDDP 100-120 mg/m<sup>2</sup> or CARBO 300-450 mg/m<sup>2</sup>) were used in 8 patients. Eight tumors in this group had axial location and were considered inoperable at presentation. In relapsed chondrosarcomas 14 patients (82%) received chemotherapy with (IFO+DOX+CDDP or CARBO). In this preliminary analysis we have evaluated the short-term results assessed by clinical/imaging response, tumor necrosis rate in surgical specimen or RECIST criteria.

**Results:** In 8 patients with locally advanced and inoperable primary chondrosarcomas no major clinical or imaging responses were seen. Among 11 operated patients no good histological responders were documented. In relapsed tumors 8 patients progressed despite chemotherapy (53%), 7 patients (47%) had clinical benefit as stable disease (5) or partial response (2). Two patients were not evaluated for response.

**Conclusions:** In primary chondrosarcoma chemotherapy had a little impact on disease evolution, especially in locally advanced inoperable tumors. Attempts to improve local response by intra-arterial administration or adding of IFO were unsuccessful. In relapsed tumors selected patients can achieve SD or PR after chemotherapy and could be considered as candidates for the second surgical remission. The impact of this combined approach on long-term results remains to be defined.

# INSTITUTIONAL VARIABLES IN THE EUROPEAN AND AMERICAN OSTEOSARCOMA STUDY EURAMOS-1: PEDIATRIC AND ADOLESCENT VS. YOUNG ADULT OSTEOSARCOMA PATIENTS.

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Stefan Bielack<sup>1,2</sup>, Jane Hook<sup>3</sup>, Gordana Jovic<sup>3</sup>, Neyssa Marina<sup>4</sup>, Sigbjørn Smeland<sup>5</sup>, Matthew R Sydes<sup>3</sup>, Jeremy Whelan<sup>6</sup>, Mark Bernstein<sup>7</sup>

Klinikum Stuttgart - Olgahospital<sup>1</sup> and University Hospital Muenster<sup>2</sup>, Germany; MRC Clinical Trials Unit<sup>3</sup> & UCL Hospitals NHS Trust<sup>6</sup>, London, UK; Stanford University Medical Center, USA<sup>4</sup>; Norwegian Radium Hospital, Oslo, Norway<sup>5</sup>; IWK Health Centre, Dalhousie University, Halifax, Canada<sup>7</sup>

**Introduction:** Osteosarcoma is a typical cancer of adolescents and young adults (AYA). We used the final enrolment data for EURAMOS-1, open for patients aged 0-40 years, in order to determine how the institutional background through which young adult patients enter "AYA-trials" is different from that of younger patients.

**Material and Methods:** Analysis of patient- and tumor-related variables as well as institutional variables and randomization rates for patients aged  $\leq 18$ yr (children and adolescents) and  $>18$ yr (young adults) at diagnosis of resectable high-grade osteosarcoma entered into EURAMOS-1/AOST0331 (NCT00134030; ISRCTN67613327; EUDRACT-2004-000242-20) between Apr-2005 and Jun-2011.

**Results:** 2,260 patients from 326 institutions were registered, including 1,108 patients from 13 European countries (AUT=28, BE=52, CH=39, CZ=9, DK=27, FIN=3, D=432, H=24, IRE=6, NL=101, N=41, SE=48, UK=298). Younger patients ( $\leq 18$ yr, median: 13yr) comprised 85% (n=1,930) of the registered population and were recruited from 93% (303/326) of trial sites (average recruitment: 6.4 pts  $\leq 18$ yr/site). Older patients ( $>18$ yr, median: 22yr) comprised only 15% of the registered population (n=330) but were recruited from 41% of trial sites (133 sites, average: 2.5 pts  $>18$ yr/site). Only 23/326 sites limited recruitment to only pts  $>18$ yr and contributed 41/330 such patients. The randomization rates were 59% (1,135/1,930) for younger and 54% (177/330) for older patients, but only 52/133 (39%) sites registering older patients managed to randomize at least one of their  $>18$  year olds, whereas 229/303 (76%) sites registering patients  $\leq 18$ yr randomized at least one of those younger patients. As expected, the proportions of males (71% vs. 57%) and of axial primaries (12% vs. 4%) were higher in older compared to younger patients, while the proportion of patients with definite and possible primary metastases was similar (24% vs. 23%).

**Conclusions:** Centralization of treatment was low overall, especially for older patients (young adults) with osteosarcoma. Most patients aged  $>18$ yr entered our trial through institutions also caring for pediatric or adolescent patients. Efforts which target "adult" oncology seem to be warranted.

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# OUTCOME OF 66 PATIENTS WITH A LATE SOLITARY LUNG METASTASIS AS FIRST RECURRENCE MORE THAN 3 YEARS AFTER INITIAL DIAGNOSIS OF OSTEOSARCOMA OF THE EXTREMITIES

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Miriam Wilhelm, M.D.<sup>1\*</sup>, Marilena Cesari, M.D.<sup>2</sup>, Katja Zils, M.D.<sup>1</sup>, Stefano Ferrari, M.D.<sup>2</sup>, Godehard Friedel, M.D.<sup>5</sup>, Leo Kager, M.D.<sup>4</sup>, Thekla v. Kalle, M.D.<sup>3</sup>, Matthias Kevric<sup>1</sup>, Thomas Kühne, M.D.<sup>6</sup>, Anna Paioli, M.D.<sup>2</sup>, Michele Rocca, M.D.<sup>2</sup>, Benjamin Sorg<sup>1</sup>, Stefan Bielack, M.D.<sup>1</sup>

<sup>1</sup>Cooperative Osteosarcoma Study Group (COSS), Klinikum Stuttgart -Olgahospital, Pediatrics 5 (Oncology, Hematology, Immunology; Gastroenterology, Rheumatology, General Pediatrics), Stuttgart, Germany

<sup>2</sup>Italian Sarcoma Group (ISG), Bone Tumor Center, Istituto Ortopedico Rizzoli, Bologna, Italy

<sup>3</sup>Department of Paediatric Radiology, Klinikum Stuttgart – Olgahospital, Stuttgart, Germany

<sup>4</sup>St. Anna Kinderspital, Vienna, Austria

<sup>5</sup>Department of Surgery, Schillerhöhe, Gerlingen, Germany

<sup>6</sup>Department of Hematology and Oncology, Basel, Switzerland

**Introduction:** Late, solitary pulmonary osteosarcoma metastases are believed to carry a favorable prognosis. We investigated this hypothesis and which factors contribute to outcome in this cohort.

**Patients and Methods:** This joint analysis of the Cooperative Osteosarcoma Study Group (COSS) and the Italian Sarcoma Group (ISG) retrospectively investigated characteristics, treatment, outcome and prognostic factors in patients with high-grade central osteosarcoma of the extremities who – after multimodal therapy and first complete surgical remission (CR1) of disease - developed a late ( $\geq 3$  years from initial diagnosis/date of biopsy) solitary lung metastasis.

**Results:** 66 evaluable patients (44 male, 22 female; median age at initial diagnosis 13 years). Lung metastases were detected via routine follow-up imaging ( $N=44/57$  with relevant data) or through symptoms ( $N=13/57$ ). Median interval of 4.4 years (range: 3.0-19.0). Characteristics of the solitary lung metastases: Median diameter 2.5 cm (range: 0.6-16 cm;  $N=56$ ); 7/41 with relevant data pleural disruption; 18/45 adjacent to pleura and 6/40 pleural effusion. All but 3 metastases were operated and a second macroscopically complete surgical remission (CR2) was achieved in 60/66 patients. In 6/65 patients with relevant data, first recurrence treatment included radiotherapy, in 22/63 chemotherapy.

Median follow up after diagnosis of first recurrence was 4.7 years (range: 0.1-20.1). Events were reported in 36 patients: No CR2 ( $N=6$ ), second recurrence ( $N=28$ ; 10/28 at the site of the first recurrence) or death in CR2 ( $N=2$ ). In all but 2/28 patients with second recurrence the interval from first to second recurrence was shorter (median: 1.2 years) than the interval from initial diagnosis to first recurrence (median: 4.4 years).

24 patients died after a median of 2.8 years from diagnosis of relapse, 42 patients were alive in CR2 ( $N=30$ ), CR3 ( $N=7$ ) or with disease ( $N=5$ ) after a median of 8.4 years. Actuarial overall survival after first recurrence at 5, 10 and 15 years was 65.1%, 57.3% and 52.9% and event free survival (EFS) 41.9%, 39.1% and 39.1%, respectively.

Positive prognostic factors for EFS were: Detection of first recurrence by imaging rather than symptoms ( $p<0.001$ ), diameter of metastasis  $<5$  cm ( $p<0.01$ ), no pleural disruption ( $p<0.05$ ), no pleural effusion ( $p=0.05$ ), no macroscopic or microscopic tumor residuals after surgery ( $p<0.01$ ). Patients not receiving chemotherapy ( $p<0.01$ ) or radiotherapy ( $p<0.001$ ) had better EFS than others, but the groups were positively selected.

**Conclusion:** Approximately one half of all patients with late solitary pulmonary metastases can become long term survivors with appropriate therapy. Our results do not support the use of chemotherapy for this indication.

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Heribert Jürgens<sup>1</sup>, Uta Dirksen<sup>1</sup>, Susanne Jabar<sup>1</sup>, Andreas Ranft<sup>1</sup>

<sup>1</sup>University Hospital, Pediatric Hematology and Oncology, Muenster, Germany

**Objectives:** The prognosis in Ewing sarcoma has improved with a current 5-year survival rate of 75% for localized disease. Survival after relapse is still poor with less than 30% surviving. The purpose of the newly established Ewing sarcoma relapse registry is to analyze the course of disease after relapse in a large cohort of Ewing sarcoma patients.

**Material and Methods:** Standardized relapse documentation was obtained from 705 Ewing sarcoma patients treated first-line according to consecutive Ewing sarcoma trials of the German Society of Pediatric Oncology and Hematology (GPOH) from 1992 to 2009. Time to relapse and progression-free survival (PFS) after first (PFS1) and second relapse (PFS2) were analyzed. PFS after relapse was defined as stable disease or better (<25% increase to smallest measurement). Patients with death of complications or death not related to cancer were censored at date of death.

**Results:** The median time from primary diagnosis to first relapse was 481 days (46-5949), 260 days from first to second relapse (7-3081), and 212 days from second to third relapse (14-1191). Median PFS after first relapse was 0.64 years (95%CI 0.58-0.70), and 0.35 years (95%CI 0.29-0.41) after second relapse. PFS1 and PFS2 at 1 year were 0.33 (SE=0.02; n=705) and 0.16 (SE=0.02; n=319). In multivariate analysis, major prognostic factors were identified as early relapse <2 years after primary diagnosis (Risk Ratios [RR] PFS1 and PFS2: 2.64 and 2.27; p<.001) and combined relapse (vs. local relapse; RR: 1.66 and 1.78; p<.001).

**Conclusions:** Progression-free survival after first and second relapse is poor especially for patients with early relapse after initial diagnosis, and for combined distant and local recurrences.



M. Cesari<sup>1</sup>, A. Paioli<sup>1</sup>, M. Colangeli<sup>2</sup>, E. L. Staals<sup>2</sup>, E. Barbieri<sup>3</sup>, S. Cammelli<sup>3</sup>, M. Alberghini<sup>4</sup>, E. Palmerini<sup>1</sup>, M. Abate<sup>1</sup>, E. Marchesi<sup>1</sup>, P. Ruggieri<sup>2</sup>, P. Picci<sup>5</sup>, S. Ferrari<sup>1</sup>

<sup>1</sup> Chemotherapy Section, Rizzoli Orthopaedic Institute, Bologna, Italy

<sup>2</sup> Department of Orthopaedic Surgery, Rizzoli Orthopaedic Institute, Bologna, Italy

<sup>3</sup> Department of Radiotherapy, S. Orsola- Malpighi Hospital, Bologna, Italy

<sup>4</sup> Department of Surgical Pathology, Rizzoli Orthopaedic Institute, Bologna, Italy

<sup>5</sup> Laboratory of Experimental Oncology, Rizzoli Orthopaedic Institute, Bologna, Italy

**Background:** Patients aged 40 years or more are usually excluded from clinical trials. For this reason information on this subset of patients are scarce.

**Patients and methods:** A retrospective analysis was carried out at our Institution. Clinical charts, imaging and histological features of patients treated at Rizzoli Institute between 1999 and 2011 with Ewing sarcoma aged 40 years or more were reviewed.

**Results:** Twenty-eight patients with Ewing sarcoma, 40 to 70 years old (median age 45 years), treated at Rizzoli Institute between 1999 and 2011 were identified. Twenty-four (86%) had localised disease, 3 patients presented with lung metastases and 1 patient with multiple metastases (bone, lung, abdominal nodes, bone marrow). Primary tumour was in the bones in 15 (57%) patients while 13 (43%) had extra-skeletal disease. Local treatment was surgery alone in 7 patients, radiotherapy in 6 and surgery plus radiotherapy in 15 patients. Two patients underwent amputation. Median dose of radiotherapy was 54 Gy. All patients received chemotherapy according to different regimens including Adriamycin (ADM), Cyclophosphamide (CTX), Etoposide (ETO), Vincristine (VCR), Actinomycine (ACT-D), Ifosfamide (IFO). Median cumulative dose of ADM was 300 mg/m<sup>2</sup>, IFO 75 g/m<sup>2</sup>, ETO 1,600 mg/m<sup>2</sup>, CTX 6,200 mg/m<sup>2</sup>, VCR 10 mg, ACT-D 7 mg. Data about chemotherapy toxicity were available in 25 patients. Haematological toxicity CTCs1 WBC grade 4 was reported in all patients. RBC and PLT transfusion were required in 14 (56%) and in 5 patients (20%) respectively. Febrile neutropenia occurred in 28% of patients and hospitalization was required in 48%. Neurological toxicity occurred in 40% of patients (grade 1 in 9 patients and grade 2 in 1). Two patients experienced grade 1 renal toxicity and 1 patient grade 4 toxicity requiring permanent dialysis. Other toxicity included congestive heart failure (1 patient), deep venous thrombosis (2), grade 2/3 mucositis (3), vomiting requiring parenteral rehydration (1). A dose-reduction toxicity-related was required in 11 patients (44%). With a follow up ranging from 7 to 154 months (median 35 months) 13 patients (48%) remained continuously free of disease, 3 patients were free of disease after relapse, 2 patients were alive with disease, 8 patients died of disease, 1 patient died of second tumor (AML) and 1 patient was lost to follow up. The 5 years disease-free survival (DFS) and overall survival (OS) were 53% and 60% respectively. Bone tumors showed better survival than tumors located in soft tissues (5-y OS 72% for Ewing sarcomas of the skeleton and 46% for extra-skeletal lesions, 5-y DFS 71% and 34% respectively). According to local treatment 5-y OS was 80% for patients treated with surgery and radiotherapy, 56% for the patients treated with radiotherapy, 29% for patients treated with surgery.

**Conclusions:** In older patients the incidence of extra-skeletal Ewing Sarcoma is high. The oncologic results are comparable with younger patients, but a higher chemotherapy toxicity must be expected.

# SYNOVIAL SARCOMA (SYSA) IN CHILDREN AND ADOLESCENTS. TREATMENT RESULTS OF FOUR CONSECUTIVE PROSPECTIVE CWS - STUDIES.

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Ewa Koscielniak<sup>1</sup>, D. Kosztyla<sup>1</sup>, I. Leuschner<sup>2</sup>, T. Dantonello<sup>1</sup>, A. Schuck<sup>3</sup>, S. Kube<sup>1</sup>, R. Ladenstein<sup>4</sup>, M. Greulich<sup>5</sup>, S. Bielack<sup>1</sup>, B. Kazanowska<sup>6</sup>, G. Ljungman<sup>7</sup>, J. Greiner<sup>8</sup>, T. Klingebiel<sup>9</sup>

<sup>1</sup>Klinikum Stuttgart, Olgahospital Stuttgart, Germany, <sup>2</sup>Dep. Pathology, Univ. of Kiel, Germany, <sup>3</sup>Institut for Radiation Oncology, Ingolstadt, Germany, <sup>4</sup>St. Anna Kinderspital, Vienna, Austria, <sup>5</sup>Diakonissenkrankenhaus, Stuttgart, Germany, <sup>6</sup>Dep. of Paediatric BMT, Oncology /Haematology, Wroclaw, Poland, <sup>7</sup>Children's University Hospital, Uppsala, Sweden, <sup>8</sup>Kinderspital St. Gallen, Switzerland, <sup>9</sup>University Children's Hospital Frankfurt, Germany

There is still much controversy about the optimal treatment for patients with SySa. Especially the role of chemotherapy is still being debated by pediatric and medical oncologists.

The CWS Group has been treating patients with SySa in the so called "RMS-like" Group together with Rhabdomyosarcoma (RMS) and soft tissue Ewing tumors (STET) since 1981, similarly to the STS ICG AIEOP. This report presents the treatment results in patients with SySa in 4 consecutive, prospective CWS Studies 86,-91, 96 and 2002P.

**Material and Methods:** 200 patients < 21 yrs have been enrolled between 1986 and 2005. Histological diagnosis was confirmed in all cases by a reference pathologist. 103 pts had initial gross total resection (IRS I and II), 81 pts primary unresected tumor (IRS III), 16 (8%) pts had distal metastases at diagnosis. 152 pts had primary tumor located at extremities. All patients received chemotherapy consisting of the four-drug regimen VAIA (Ifosfamide, Actinomycin D, Doxorubicine, Vincristine) or in CWS-91 the five-drug regimen EVAIA (plus VP16): adjuvant 6 cycles, neoadjuvant 9 cycles. The cumulative dose of Doxorubicine varied slightly between the studies. 146 pts were irradiated.

**Results:** 193 pts achieved complete remission, and 48 pts (25%) relapsed. 24/56 (43%) pts who received primary chemotherapy and for whom response could be evaluated, showed tumor volume reduction > 33% after 3 therapy cycles. In primary localized disease the local relapse rate LRR (isolated and combined) was 14%, metastatic relapse 10%, combined 2%. The LRR rate in irradiated patients IRS I-III was 12%, in non-irradiated pts 23% (n.s). With a median follow up of 7,5 yrs (2,4-15,7) the EFS for localized disease at 5 yrs was 77%, OS 88%, for metastatic disease 25% and OS 31% respectively. EFS and OS rates at 5 yrs by IRS Group were 85/95%, 82/90% and 68/82% respectively. Tumor size, invasiveness, IRS group (I, II vs. III) and irradiation correlated significantly with EFS (but not - local relapse free survival LRFS) in univariate analysis in patients with localized disease whereas age, sex, histology (biphasic vs. monophasic), site, and trial did not. In multivariate analysis tumor size and irradiation remained relevant for EFS.

**Conclusion:** Patients with localized disease had a good cure rate whereas only 25% of patients with metastatic disease remained disease free at 5 yrs. Our EFS rates compared favorably with other large published series suggesting that treatment on prospective multimodal trials results in better outcome. It is however still unclear whether chemotherapy could be omitted in young pts with small, noninvasive tumors. This question could only be answered by an international randomized multicenter study.

# BONE METASTASES IN SOFT TISSUE SARCOMA PATIENTS: A SURVEY OF NATURAL, PROGNOSTIC VALUE AND TREATMENT.

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Bruno Vincenzi<sup>1</sup>, Daniele Santini<sup>1</sup>, Gaia Schiavon<sup>2</sup>, Anna Maria Frezza<sup>1,3</sup>, Palma Dileo<sup>3</sup>, Marianna Silletta<sup>1</sup>, Francesco Bertoldo<sup>4</sup>, Giuseppe Badalamenti<sup>5</sup>, Giacomo G. Baldi<sup>6</sup>, Stefania Zovato<sup>7</sup>, Rossana Berardi<sup>8</sup>, Franco Silvestris<sup>9</sup>, Marco Tucci<sup>9</sup>, Jeremy Whelan<sup>3</sup>, Roberto Tirabosco<sup>10</sup>, Angelo Paolo Dei Tos<sup>11</sup>, Giuseppe Tonini<sup>1</sup>.

<sup>1</sup> Dipartimento di Medicina Oncologica, Università Campus Bio-Medico di Roma, Rome, Italy;

<sup>2</sup> Department of Medical Oncology, Erasmus University Medical Center - Daniel den Hoed Cancer Center, Rotterdam, Netherlands;

<sup>3</sup> University College of London Hospital, London, England;

<sup>4</sup> Department of Biomedical and Surgical Sciences, University of Verona, Verona, Italy;

<sup>5</sup> Medical Oncology, University of Palermo, Palermo, Italy;

<sup>6</sup> Medical Oncology, Civil Hospital, Pisa, Italy;

<sup>7</sup> Unità Tumori Ereditari, Istituto Oncologico Veneto, IRCCS, Padova, Italy;

<sup>8</sup> Clinica di Oncologia Medica, A. O. Ospedali Riuniti-Università Politecnica delle Marche, Ancona, Italy;

<sup>9</sup> University of Bari, Bari, Italy;

<sup>10</sup> Royal National Orthopaedic Hospital, London, London, England;

<sup>11</sup> Azienda ULSS 9 Treviso, Treviso, Italy

**Background:** Given the limited data currently available in the literature, we surveyed the natural history of bone metastases in patients affected by soft tissue sarcoma (STS).

**Methods:** This multicenter, retrospective, observational study evaluated data from 135 patients with STS metastatic to the bone who presented between 2001 and 2011. For all patients, we recorded the primary tumor histological subtype, bone metastases characteristics (onset, site), type of treatment received (surgery, radiotherapy, zoledronic acid), type and frequency of skeletal related events (SRE) and disease outcome.

**Results:** The most represented histological subtypes among the enrolled patients were leiomyosarcoma (27%), angiosarcoma (13%) and spindle cell sarcoma (8%). The spine was the most common site for bone involvement (51%), followed by hip/pelvis (20%), long bones (15%) and other sites (14%). In 27% of cases, bone metastases were present at the time of diagnosis. Fifty-four patients (40%) developed SREs and the median time to first SRE (if developed) was 4 months (range 1-9 months). The most common SRE was the need for radiotherapy, occurring in 28% of patients, followed by pathologic fracture (22%). Patients survived for a median of 6 months (range 1-14 months) after bone metastases diagnosis. The occurrence of a SRE was associated with decreased overall survival (OS) ( $P=0.04$ ). A subgroup analysis revealed that zoledronic acid significantly prolonged median time to first SRE (5 versus 2 months;  $P = 0.002$ ). Conversely, it did not determine an improvement in terms of OS, even if a favorable trend was identified (median: 7 versus 5 months, respectively;  $P = 0.105$ ).

**Conclusions:** This study illustrates the burden of bone disease from STS and supports the use of zoledronic acid in this setting.

# ISPINAL METASTASES THERAPY (ISMT), THE NEW INTERACTIVE VERSION OF THE ALGORITHM FOR DECISION-MAKING PROCESS OF SPINE METASTATIC DISEASE

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Gasbarrini Alessandro MD\*, Colangeli Simone MD\*, Bandiera Stefano MD\*, Barbanti Brodano Giovanni MD\*, Cappuccio Michele MD<sup>c</sup>, Cuzzocrea Fabrizio MD<sup>d</sup>, Pellisè Ferran MD\*, Tancioni Flavio MD<sup>e</sup>, Terzi Silvia MD\*, Varga Peter Paul MD<sup>f</sup> and Boriani Stefano MD\*

\*Rizzoli Orthopaedic Institute, <sup>c</sup>Ospedale Maggiore, <sup>d</sup>Policlinico San Matteo, <sup>e</sup>Hospital Vall d'Hebron, <sup>f</sup>Humanitas Istituto Clinico, <sup>^</sup>Department of Spinal Disorders  
Bologna, Pavia, Barcelona, Milano, Budapest  
Italy, Spain, Hungary

**Objectives stating concisely why the study was conducted:** New interactive version of the algorithm for decision-making process of spine metastatic disease is proposed by Author's with the objective to spread this flow chart in simple and effective manner.

**Materials and methods:** The decision making process includes: anesthesiological evaluation, sensitivity to medical and radiation oncology treatments, neurological condition, pathological fractures, systematic spread of the disease and possible treatment. The treatment options are: decompression and fixation, debulking, en bloc excision, non surgical treatment.

In all cases treated by decompression and fixation or debulking, proposed an preventive embolization of the lesion to reduce the bleeding during the surgery.

In September 2009 started a Multicentric prospecting study to evaluation of the algorithm in the treatment of spinal metastases. We propose the preliminary results on 246 patients enrolled in this study to 1 year of follow up.

**Results:** In 80% of cases (196 of 246), the treatment performed was the same as proposed by the flowchart. In 185 (85%) patients evaluated on 217 (28 patients excluded for incomplete data) that performed the treatment proposed by algorithm, the Surgeons of the Centres involved in the study obtained a good result according their experience. In 50 cases (20%) the algorithm was not followed, usually to prevent overtreatment (32 cases). In these patients that were performed an overtreatment the opinion of the Surgeons involved in the study was that a good result was obtained in 21 on 32 cases (65%), while in the group of patients undertreatment the result was good in 12 on 18 cases (67%).

**Conclusion:** In the study proposed the principal objective of the Authors is to taste the applicability and reproducibility of the algorithm. The principal result obtained is that there is a common opinion from Surgeons of the different Centres about a good applicability and reproducibility of the algorithm in the treatment of patient affected by spinal metastases.

New interactive version of the algorithm for decision-making process of spine metastatic disease is proposed by Authors.

# THE EVALUATION OF FOUR PROGNOSTIC MODELS FOR PREDICTING SURVIVAL IN PATIENTS WITH SYMPTOMATIC SPINAL METASTASES

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Bollen L.<sup>1</sup>, de Ruiter G.C.W.<sup>2</sup>, Lobatto D.<sup>1</sup>, Arts M.<sup>3</sup>, Pondaag W.<sup>2</sup>, Peul W.C.<sup>2</sup>, Dijkstra P.D.S.<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Leiden University Medical Center Leiden, the Netherlands.

<sup>2</sup>Department of Neurosurgery, Leiden University Medical Center, Leiden, the Netherlands.

<sup>3</sup>Department of Neurosurgery, Medical Center Haaglanden, The Hague, the Netherlands.

**Objectives:** Accurate prediction of survival in patients with symptomatic spinal metastases (SSM) is of the utmost importance in order to ensure a proper relation between extent of surgery and actual survival time. In this study we evaluated the accuracy of four commonly used prognostic models.

**Materials and Methods:** All patients who were surgically treated for SSM between January 2001 and December 2010 were included in this bi-center retrospective study (n=106, male n=53, female n=53, mean age  $59.1 \pm 10.9$  years). Medical records were reviewed to obtain seven items necessary to utilize scoring systems according to Tomita (modified), Bauer (modified), Tokuhashi (revised) and Van der Linden (modified). Most common primary sites of cancer were breast (n=25), lung (n=20), kidney (n=19) and prostate (n=11). Scoring systems were adapted based on median survival times for each type of primary tumor. Based on their respective scores, all patients were arranged in groups as defined by the scoring systems. Survival analysis and overall comparisons were performed using Kaplan-Meier survival analysis and univariate log-rank tests.

**Results:** Overall median survival is 10.7 months with a minimum follow-up of 11 months and no loss to follow-up. All scoring systems have a significant overall predictive value for survival. Bauer (modified) and Van der Linden (modified) are unable to differentiate between medium- and long-term survival. Tokuhashi (revised) is able to differentiate between short- and long-term survival but not between medium- and long-term, nor medium- and short survival. Tomita (modified) is the only score able to accurately reflect survival in all three groups (short-medium  $p=0.045$ , short-long  $p<0.001$  and medium-long  $p<0.001$ , see Figure 1).

**Conclusions:** When considering surgery for symptomatic spinal cord metastases, clinicians must ensure that no needlessly extended surgery takes place in those patients that do not live long enough to fully benefit from the intervention. An accurate scoring system can be a helpful tool. The modified Tomita score is the most reliable score for predicting survival in patients with SSM.

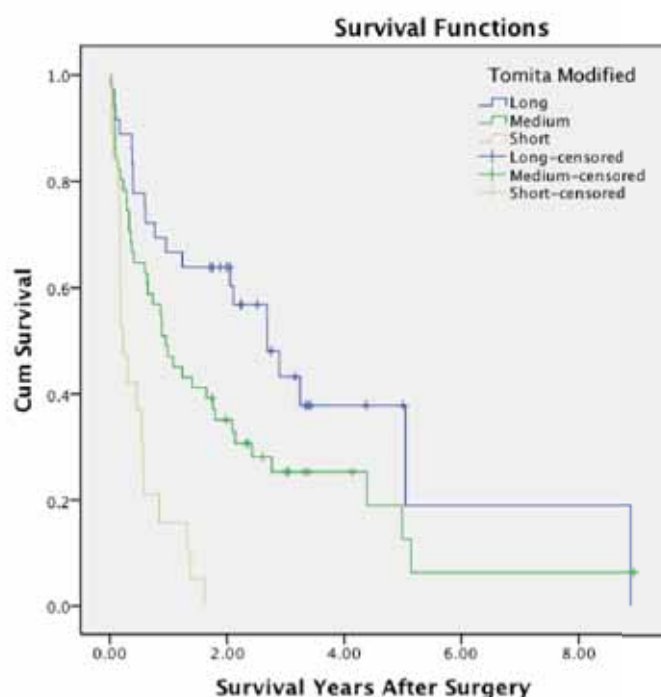


Figure 1. Survival function for the modified Tomita scoring system

Dardic M<sup>1</sup>, Wibmer C<sup>1</sup>, Berghold A<sup>3</sup>, Stadlmueller L<sup>3</sup>, Zacherl M<sup>1</sup>, Leithner A<sup>1</sup>, Hofmann G<sup>2</sup>

<sup>1</sup>Department of Orthopaedic Surgery,

<sup>2</sup>Department of Internal Medicine, Division of Oncology, and

<sup>3</sup>Institute for Medical Informatics, Statistics and Documentation at  
Medical University of Graz  
Graz, Austria.

**Objectives:** Patients with advanced cancer disease frequently develop metastases in their vertebral column. Through pain, neurological dysfunction and mechanical instability, these metastases can severely decrease patient's function and quality of life. Correct estimation of the survival time is crucial in order to implicate the right course of palliative treatment. Based on concluded studies at our department, we conducted a sequel evaluation with an updated dataset in order to analyze the parameters and prognostic scoring systems in more recently treated patients.

**Materials and Methods:** This retrospective study included 196 patients with confirmed spinal metastases of diverse cancer origin treated either surgically (35%) or conservatively (65%) between 2005-2010. Possible prognostic factors, such as primary tumor, general condition (Karnofsky Performance Scale KPS), visceral metastases, numbers of spinal and extra spinal metastases, pathological fracture, pre- and post-op. neurologic status, spinal surgery and others were evaluated retrospectively. We estimated the survival time from the date of confirmed spinal metastases to the date of death or last follow-up. (minimum follow up: 12 months). Statistical analysis comprised univariate and stepwise multivariate Cox regression (p-value  $\leq 0.05$  regarded significant) and Kaplan-Meier-Curve.

**Results:** Median overall survival for all patients was 7 months (minimum 5 days, maximum 70 months). At the time of analysis 178 patients had deceased (91%) and 18 patients were still alive (9%). Using univariate survival analysis primary tumor, visceral metastases, KPS, number of spinal metastases, spinal surgery, gender and age presented statistical significance. In stepwise multivariate analysis primary tumor, visceral metastases, KPS, number of spinal metastases and spinal surgery showed significant influence on survival. All evaluated scoring systems (Tokuhashi original and revised, Tomita, van der Linden and Bauer original and modified) showed significant impact in estimating the survival.

**Conclusions:** Our study showed reliability of the analyzed scoring systems in a recent patient collective. Based on these results we recommend the Bauer modified score for its impact and additionally for its simplicity.



# MALIGNANT BONE TUMORS OF THE FOOT HAVE A DIFFERENT BIOLOGICAL BEHAVIOR THAN TUMORS AT OTHER SKELETAL SITES

006

AH Krieg<sup>1</sup>, M Brotzmann<sup>1</sup>, D Baumhoer<sup>2</sup>, F Hefti<sup>1</sup>

AH Krieg, MD, Orthopaedic Surgeon

<sup>1</sup>University Children's Hospital (UKBB), Basel, Switzerland

<sup>2</sup>Bone Tumor Reference Center at the Institute of Pathology, University Hospital, Basel, Switzerland

**Introduction:** In a retrospective study, we analyzed the delay in diagnosis and tumor size of malignant bone tumors of the foot. To our knowledge, there is a lack of information regarding these factors in the literature. We compared the oncological and surgical long-term results with identical tumors at other anatomical sites in order to analyze the biological behavior of malignant bone tumors that are found in the foot.

**Methods:** Thirty-two patients (17 male, 15 female) with a histologically proven malignant bone tumor between the years 1969–2008 were included in the study. The median age was 41.2 years (range 9.8–72.9 years), and median follow up was 11.9 years (3–26.3 years). Fifteen chondrosarcomas, nine osteosarcomas, and eight Ewing sarcomas were included in the study.

**Results:** There was an overall median time gap of 10 months (range 3–128 months) between the beginning of symptoms and diagnosis in the study group. Ewing sarcoma presented with the longest delay in diagnosis (median 18 months, range 3–34 months), followed by osteosarcoma (median 15 months, range 1–23 months) and chondrosarcoma (median 7.5 months, range 1–128 months). The delay in diagnosis of these tumors was significantly longer than that of equivalent tumors at other skeletal sites, but the 5- and 10-year survival rates and the occurrence of distant metastases were comparable. In contrast, the average size of foot tumors was 5- to 30-fold less than that of tumors analyzed at other skeletal sites.

**Conclusions:** This study indicates that sarcomas of the foot present the distinct biological behavior of slower growth compared to tumors at other skeletal sites.

Chigusa Sawamura<sup>1,2</sup>, Seiichi Matsumoto<sup>2</sup>, Keisuke Ae<sup>2</sup>, Shimoji Takashi<sup>2</sup>, Atsushi Okawa<sup>1</sup>

1. Orthopaedics, Tokyo Medical and Dental University, Tokyo, Japan.
2. Orthopaedics, Cancer Institute Hospital of Japanese Foundations for Cancer Research, Tokyo, Japan.

**Objective:** NCCN (National Comprehensive Cancer Network) guidelines suggests that follow up for low-grade soft tissue sarcomas should be every 3-6 months for 2-3 years then annually and for high-grade sarcomas every 3-6 months for 2-3 years then every 6 months for the next 2 years then annually, although there are very limited evidence to support this strategies. We evaluated incidence of local recurrence and metastasis for different time periods to see the trend of events. We expected higher incidence of local recurrence and metastasis within the first 2 years.

**Materials and Methods:** Patients diagnosed with soft tissue sarcomas and who underwent surgical excision of tumor at Cancer Institute Hospital in Tokyo between 1978 to 2008 were retrospectively reviewed. Patients who had metastasis at diagnosis (M1) were excluded. Age, histologic diagnosis, grade, tumor location, size, adjuvant treatments were reviewed for each patient. Incidence of local recurrence and metastasis were calculated for every 2-year period and presented per 1000 person-years.

**Results:** 881 patients with a median age at diagnosis of 52-years were eligible for analysis. 32 % of patients were diagnosed with malignant fibrous histiocytoma, 15% had liposarcoma and 12% had well differentiated liposarcoma. 92 patients (10%) developed local recurrence at a median time of 18.5 months and 90% of patients had local recurrence within 5.1 years, 95% in 7.3 years and 99% in 20.4 years. 195 patients (22%) developed distant metastasis at median time of 11.7 months and 90% of patients had metastasis within 4.1 years, 95% in 7.1 years and 99% in 20.5 years respectively. The rate of local recurrence was 38/1000 person-years (Fig.1) and for metastasis was 103/1000 person-years in first 2 years (Fig.2). These incidences were higher than those of after 2 years and this trend was more evident for incidence of metastasis than that of local recurrence.

**Conclusions:** Since incidence rate of local recurrence and metastasis were higher at first 2 years, it is reasonable to follow up frequently during this period. 95% of local recurrence and metastasis would be found if patients were followed up for a period of 8 years. Follow-up beyond 10 years does not yield a sufficient number of recurrences or metastases to warrant this further monitoring.

Fig. 1

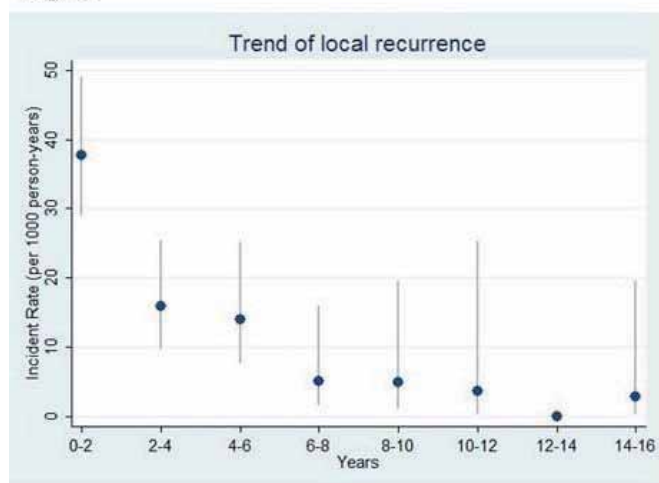
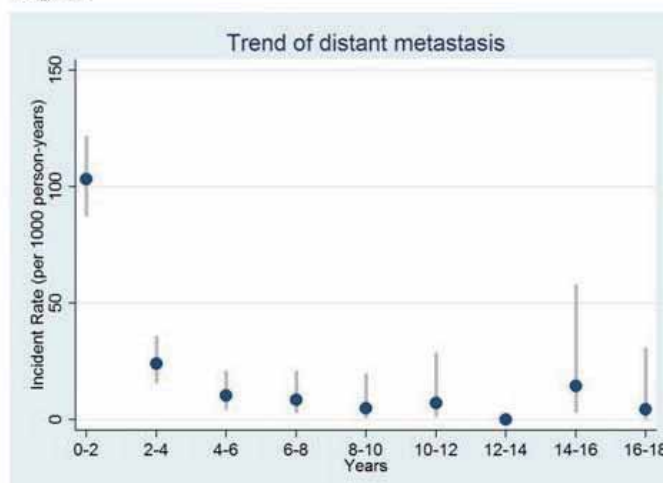


Fig. 2



# PSYCHO-ONCOLOGICAL ASPECTS IN THE TREATMENT OF TUMOR PATIENTS AT ORTHOPEDIC TUMOR CENTERS IN GERMAN-SPEAKING COUNTRIES

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U. Lenze\*, F. Pohlig\*, G. Gradl\*, J. Schauwecker\*, H. Rechl\*, P. Herschbach\*, R. von Eisenhart-Rothe\*

\* Department for Orthopedics, Klinikum rechts der Isar der Technischen Universität München

\* Roman Herzog Comprehensive Cancer Center (RHCCC), Klinikum rechts der Isar der Technischen Universität München

**Introduction:** Psycho-social distress is a common problem in a considerable number of patients suffering from malignant diseases. However, in German-speaking countries psychosocial screenings haven't been implemented into diagnosis related guidelines for the treatment of orthopedic tumor patients.

Therefore, aim of the study was to evaluate the significance of psycho-oncology in orthopedic institutions specialized in musculoskeletal tumors as well as the opinion and clinical experience of the treating physicians.

**Methods:** In total 60 orthopedic institutions in Germany, Austria and Switzerland were recruited from the German society for Orthopedics and Orthopedic Surgery as well as from the internet. Data regarding the role of psycho-oncology as well as individual experiences of the physicians working at the enrolled institutions were assessed and analyzed by a newly developed, standardized questionnaire. To detect specific, demographic differences results were additionally analyzed according to gender, age ( $\leq 40$ ,  $> 40$  years) and professional experience ( $\leq 10$ ,  $> 10$  years).

**Results:** A total of 118 physicians from 47 of the enrolled 60 institutions (85,5%) participated. The majority of respondents (57,3%) indicated that psycho-social aspects play a minor role within the tumorboards of the enrolled institutions. Significant differences between professional experience groups were obtained regarding the wish for psychosocial treatment in case of own illness ( $p=0,032$ ) and the difficulty of addressing the patients' feelings. Significant differences with respect to age groups and gender were not obtained.

**Conclusion:** Although orthopedic physicians deemed psycho-oncology important little attention is paid within the tumorboards of the enrolled institutions. To ensure a holistic approach to the treatment of orthopedic tumor patients psycho-oncological aspects should be implemented more in clinical practice and diagnosis related guidelines.

# ERCC1 PROTEIN EXPRESSION PREDICTS SURVIVAL IN PATIENTS WITH HIGH-GRADE, NON-METASTATIC OSTEOSARCOMA TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Claudia Maria Hattinger<sup>1</sup>, Massimo Serra<sup>1</sup>, Emanuela Palmerini<sup>2</sup>, Federica Sella<sup>1</sup>, Stefano Zagnoni<sup>1</sup>, Stefania Benini<sup>3</sup>, Marco Alberghini<sup>3</sup>, Piero Picci<sup>1</sup>, Stefano Ferrari<sup>2</sup>

<sup>1</sup>Laboratory of Experimental Oncology, <sup>2</sup>Chemotherapy Ward of Musculoskeletal Tumors and <sup>3</sup>Anatomy and Pathological Histology, Orthopaedic Rizzoli Institute, Bologna, Italy

**Objectives:** Cisplatin is an important drug of standard neo-advjuvant chemotherapy protocols for patients with high-grade non-metastatic osteosarcoma. Positive excision repair cross-complementation group 1 (ERCC1) protein expression has been reported to be associated with resistance to cisplatin and to influence survival in a number of human neoplasms. To assess ERCC1 protein expression in high-grade osteosarcoma and to evaluate its possible clinical impact, immunohistochemistry was performed on surgical biopsies from patients enrolled in two different neoadjuvant chemotherapy protocols based on the use of cisplatin in association with doxorubicin, methotrexate and ifosfamide. Immunohistochemical data were correlated with clinicopathologic parameters and survival.

**Materials and Methods:** Immunohistochemistry was performed using the anti-ERCC1 monoclonal antibody 8F1 (abcam) with a biotin-avidin peroxidase and diaminobenzidine detection system. Samples were scored as negative (percentage of positive nuclei ranging from 0 to 10%) or positive (more than 10% of positive nuclei) for ERCC1 protein expression.

In a first study, immunohistochemical detection of ERCC1 was performed on tissue sections of tumour biopsies from 31 patients with non-metastatic, high-grade osteosarcoma of the extremities enrolled in the ISG/A/OSS study protocol from 2007 to 2009 (median follow-up 39 months). The findings obtained in this series were validated on tumour biopsies from 68 Italian patients treated according to the ISG/SSG 1 protocol from 1997 to 2000 (median follow-up 136 months, 5-year probability of EFS 59%).

The ISG/A/OSS protocol included high-dose ifosfamide only in the post-operative protocol for patients who poorly responded to a pre-operative therapy consisting of high-dose methotrexate, cisplatin and adriamycin. The the ISG/SSG 1 protocol included all four drugs, both pre- and postoperatively, administered with different schedules according to the extent of tumor necrosis after the preoperative treatment.

**Results:** In the ISG/A/OSS patients, immunohistochemical positivity for ERCC1 was found in 8/31 (26%) samples. The event-free survival (EFS) rate was 25% in ERCC1-positive cases and 65% in ERCC1-negative patients ( $P = 0.01$ ). The significant association between ERCC1 positivity and worse clinical outcome was evident also for overall survival (OVS), which was 50% in ERCC1-positive and 95% in ERCC-1 negative patients ( $P = 0.003$ ).

In the validation series, 22/68 ISG/SSG 1 patients (32%) patients were scored as positive for ERCC1 expression. The 5-year EFS was 36% in ERCC1 positive and 69% in ERCC1 negative patients ( $P = 0.026$ ). ERCC1 positivity was also associated with worse OVS, which was 50% and 74% in ERCC1-positive and negative patients, respectively ( $P = 0.047$ ).

Correlation analyses for ERCC1 positivity and clinicopathological parameters revealed a statistically significant association between high serum LDH levels and ERCC1 positivity (Fisher's test,  $P = 0.012$  for ISG/A/OSS patients and  $P = 0.025$  for ISG/SSG 1 patients) and a trend towards higher relapse rate in ERCC1-positive cases in both studies.

**Conclusions:** ERCC1 positivity assessed by immunohistochemistry on biopsies tissue sections is predictive for outcome of patients with non-metastatic, high-grade osteosarcoma treated with cisplatin-including chemotherapy. The association between ERCC1 positivity and worse survival suggests an important role of ERCC1 in the resistance to cisplatin and/or in treatment unresponsiveness in human osteosarcoma patients.

## Acknowledgements

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# MASSIVE GENOMIC REARRANGEMENT AND CHROMOSOMAL ALTERATION STAGING ARE CRUCIAL FACTORS IN OSTEOSARCOMA PROGNOSIS

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Smida J. 1-2, Baumhoer D. 3, Rosemann M. 4-5, Bielack S. 6, Korsching E. 7, Burdach S. 2, Jundt G. 3, Atkinson M.J. 4-5, and Nathrath M. 1-2

1 Clinical Cooperation Group Osteosarcoma, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Germany

2 Department of Pediatrics, Technische Universitaet Muenchen and Pediatric Oncology Center, Germany

3 Bone Tumor Reference Center at the Institute of Pathology, University Hospital Basel, Switzerland

4 Institute of Pathology and 5 Institute of Radiation Biology, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Germany

6 Klinikum Stuttgart Olgahospital, Pediatrics 5 - Oncology, Hematology, Immunology, Germany

7 Institute of Bioinformatics, University of Muenster, Germany

**Introduction:** Based on a study performed in 45 pretherapeutic osteosarcoma samples we found a clear correlation between genomic rearrangement and the outcome of disease. We proposed a chromosomal alteration staging (CAS) system, which was shown to have superior predictive potential compared to the histologic regression grading. Tumors were defined as CAS positive, when at least two out of four genomic alterations including amplifications of chromosome 6p21, 8q24 (harboring *MYC*) and 12q14 (harboring *CDK4*) as well as LOH of 10q21.1 occurred.

**Strategy and Results:** To validate these findings we investigated an independent collective of 58 high-grade osteosarcomas samples using most recent methods (SNP Arrays 6.0, Affymetrix). This verification supports our previous results that the genomic rearrangement and the CAS system have prognostic impact for osteosarcoma patients. Furthermore, we were able to examine the previously described regions with striking higher resolution, including a new dimension in quality of CNV (copy number variations) analysis. Three out of four CAS components were found to be adequately distributed in the new collective. The primarily observed LOH frequency (exemplarily at 10q21.1) could not be verified because of the use of a new analysis technique, therefore the LOH component of the CAS system has to be redefined as massive genomic rearrangement of specific CNV patterns.

**Summary:** The CAS system could be verified in an independent collective and proofed to predict the prognosis very accurately in more than 100 osteosarcomas already at the time of initial diagnosis. Therefore, this molecular staging system might help to modify neoadjuvant treatment strategies in molecular high risk patients in future treatment protocols.

# TENOVIN 6, A NOVEL SIRTUIN DEACETYLASE INHIBITOR WITH ANTI TUMOR ACTIVITY IN SYNOVIAL SARCOMA AND RABDOMYOSARCOMA.

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Bertha Brodin<sup>1\*</sup>, Wessen Maruwge<sup>1</sup>, Pdraig D'Arcy<sup>1</sup>, Barry Wolahan, Asle Hesla<sup>2</sup>, and 3Sonia Lain.<sup>3</sup>

<sup>1</sup>Department of Oncology and Pathology, <sup>3</sup> Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, <sup>2</sup>Orthopedic Tumor Surgery, Karolinska University Hospital, Stockholm, Sweden.

Sirtuins are a subclass of histone deacetylases (class III), with histone and non-histone substrates. They act in a NAD<sup>+</sup> dependent manner and are involved in several cellular processes including metabolism, cell survival, muscle differentiation and aging.

In the present study, we have evaluated the activity of tenovin 6, a newly discovered, sirtuin deacetylase inhibitor and p53 activator, in preclinical models of synovial sarcomas and rhabdomyosarcomas with wild type p53. In vitro, tenovin-6 inhibited tumor cell proliferation and restored trans-activation function of p53. In SCID mice, tenovin 6 significantly reduced tumor growth. The treated tumors were characterized by increased nuclear p53 and sirtuin 2 expression.

Interestingly, combination treatment of rhabdomyosarcoma and synovial sarcoma cells with tenovin-6 induced an increased response to the multikinase inhibitor Sorafenib. Our results show that tenovin 6 is a drug with therapeutic potential for synovial sarcoma and rhabdomyosarcoma and indicate that the pharmacologic blockade of SIRT 1 can be used to restore response in sarcomas that develop resistance to kinase inhibitors.



## INVESTIGATING THE ROLE OF A DUAL KINASE INHIBITOR, OSI-906 IN EWING SARCOMA PRIOR TO APPLICATION TO A PHASE II CLINICAL TRIAL.

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*Branford White HA, Barnes DJ, Buehnemann C, Li S, Yu H, Noble A, Scotlandi K, de Alava E, Hassan AB.*

Treatment with a monoclonal antibody to the IGF1 Receptor has demonstrated tumour regression in approximately 30% of patients with Ewing Sarcoma. This aggressive primary bone tumour affecting young adults is characterised by the presence of the chimeric transcription factor EWS-FLI1 in 90% of patients resulting in activation of the Insulin Growth Factor (IGF) pathway via IGFBP3 suppression. The mechanism responsible for such a diverse response to an IGF1R inhibitor remains obscure however recent evidence suggests that suppression of the IGF1 Receptor (IGF1R) is accompanied by a compensatory upregulation of Insulin Receptor (IR) which drives the downstream PI3K and MEK/ERK pathways. We postulate that using dual kinase inhibitor to both IGF1R and IR will alter proliferation and promote apoptosis of Ewing sarcoma as well as demonstrate heterogeneity of response between different cell lines.

Using well characterised Ewing sarcoma cell lines (EuroBoNet) we first optimised an assay with read outs of proliferation, apoptosis, cell cycle, and the cell surface markers of IGF1 and Insulin Receptors. These were then combined and cells analysed using flow cytometry for differing responses to OSI-906, a dual kinase inhibitor alone and in combination with common chemotherapeutic agents such as doxorubicin.

Our validated cell labelling assay demonstrated that OSI-906 affects both proliferation and apoptosis in Ewing cancer cells and alters sensitivity of cell lines when combined with mainstay chemotherapeutics. This outcome therefore supporting the role for a stratified approach in a clinical trial.

Maria Cristina Manara,<sup>1,2</sup> Cecilia Garofalo,<sup>1,2</sup> Caterina Mancarella,<sup>1,2</sup> Piero Picci,<sup>1</sup> and Katia Scotlandi<sup>1,2</sup>

CRS Development of Biomolecular Therapies, Laboratory of Experimental Oncology, Orthopaedic Rizzoli Institute, Bologna, Italy

**Background:** Identification of new active agents against sarcoma is considered an important challenge in medical oncology. We previously reported a potent activity of ET-743 (Trabectedin, Yondelis) against both drug-sensitive and drug-resistant (multidrug-resistant, methotrexate- and cisplatin-resistant) bone tumor cells. Ewing sarcoma (EWS) cells appeared to be particularly sensitive to the effects of this drug. However ET-743 exposure over sustained periods of treatment will result in the development of drug resistance. The analysis of molecular mechanisms responsible for resistance to ET-743 in EWS cells identified increased IGF-IR signaling, together with higher P-glycoprotein expression as significant contributors to ET-743 resistance.

**Objectives:** Effects of ET-743 and of its analog Zalypsis was evaluated in a panel of EWS cell lines, as single agents and in combination with conventional agents (Vincristine, Doxorubicin, Gemcitabine). In addition combinatory treatments with specific inhibitors of IGF-IR (Hab AVE1642, TKI NVP-AEW541), was assessed to define future possible therapeutic option for EWS patients refractory to conventional agents.

**Results:** Both ET-743 and of its analog Zalypsis induced a slower progression through the different phases of the cell cycle in EWS cells. ET-743 showed higher efficacy than Zalypsis. In addition a differentiative effects was observed, as indicated by increased expression of markers of neural differentiation (beta-III tubulin and H-neruofilament) and by the appearance of a phenotype "neurite-like" following treatment. Drug-drug interactions with conventional drugs showed a synergistic associations with doxorubicin, while additive effects were observed with vincristine and Gencitabine. Very positive associations were observed when ET-743 or Zalypsis were combined with anti-IGF-1R agents (Hab AVE1642, TKI NVP-AEW541), indicating that IGF-IR system is involved in regulating EWS cell sensitivity to these drugs.

**Conclusions:** Overall, these results encourage the inclusion of this drug in the treatment of patients with Ewing's sarcoma. Moreover, association with several available IGF-IR inhibitors may represent a promising and concrete answer to overcome resistance for patients refractory to conventional agents. (Grants: AIRC IG-10452 to KS, MinSan bando 2009; EuroSarc).

## THE CONCEPT OF INDUCED MEMBRANE FOR RECONSTRUCTION OF LONG BONE DEFECTS – CASE REPORT

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S Dadia, Y Gortzak, Y Kollender, J Bickels, I Meller

**Objective:** The reconstruction of wide long bone diaphyseal defects is often a major challenge in limb salvage whatever the etiology of bone loss. The reconstruction methods common used are: diaphyseal implants, vascular fibular graft and bone transport. As these procedures do not always succeed, there is an uncommon option, lately introduced by Masquelet & Begue (2010), of an induced membrane concept as a salvage procedure.

This case report was aiming to check if induced membrane could successfully be used as salvage where other options failed.

**Materials:** 8 year old boy, with stage II B osteosarcoma in his left mid femur after neo adjuvant chemotherapy and intercalary resection of his mid femur (14cm), reconstructed with micro vascular fibular graft. Diagnosed with acute deep infection of the graft after a month. 3 consecutive procedures of washout, debridement & aggressive antibiotic treatments led to 17cm bone defect after removal of the infected graft.

Induced membrane concept was decided to be introduced: A) Insertion of cement spacer into the bone defect. Simultaneously remaining bone fixed with Ilizarov frame & IM nail. B) 3 months later, after additional clearance of the infection, spacer was removed and induced membrane which grew over the cement was left in place. C) The cavity was filled by morcellized cancellous bone autograft harvested from the Iliac crest. D) The membrane sutured over the bone graft.

**Results:** 4 months after last procedure, the patient did not show any sign of deep infection (clinical & laboratory). Consecutive x-rays shows a good and progressing bone healing in the membrane chamber. Patient is ambulating with no-weight bearing with good thigh muscle strength and hip & knee motion.

**Conclusions:** In our case study, induced membrane concept was a good alternative salvage for large bone defect. 4 months after bone grafting, there is good bone regeneration in the membrane cavity. We can assume that the role of cement as biological spacer, inducing a foreign body surrounding membrane, which then after is filled, the membrane avoids resorption of the cancellous bone and has a positive effect of healing of the auto graft.

There is further need to see the future consolidation of the bone. But, although this is a single case report, it suggests a potential treatment which seems to be interesting to investigate even for primary cases.

# THE ROLE OF THE MUSCULOSKELETAL TISSUE BANK IN LIMB SALVAGE SURGERY OF CHILDREN: ANALYSIS OF RECENT RIZZOLI INSTITUTE EXPERIENCE

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Marco Manfrini, Marco Colangeli, Luca Boriani, Massimiliano De Paolis, Pietro Ruggieri & Pier Maria Fornasari

Istituto Ortopedico Rizzoli, Bologna, Italy

**Introduction:** During the 1980s, as massive bone allografts (MBA) started to be used for limb salvage procedures, orthopedic oncology became one of the primary specialties to promote the development of musculoskeletal tissue banking.

At the Rizzoli Institute, the pioneering bone bank initiated in 1962 was transformed in 1997 into the Cell and Musculo-Skeletal Tissue Bank (CMSTB), a non-profit unit of the regional-national health care system, that follows European Union standards and guidelines and is recognized by the Italian Drug Agency and National Transplant Center.

**Objectives:** To analyze the current impact of bone banking in limb salvage procedures, especially in pediatric population.

**Methods:** This retrospective study from 2005-2009 involved analysis of CMSTB files and all limb salvage procedures performed at the Rizzoli Institute in children below age 15 with primary malignant tumors of humerus, femur, and tibia.

**Results:** During this five year period, CMSTB harvested 317 cadaveric donors from which 3832 bone and tendon specimens were stored. Some specimens were further processed into freeze-dried grafts, frozen morcellized bone, and/or demineralized bone matrix. MBAs were utilized for surgical reconstruction in 639 patients.

In the same period, at Rizzoli Institute, limb salvage surgery was performed in 111 skeletally immature patients (mean age 10,3 years; range 4-14). Histological diagnoses included 82 (74%) osteosarcomas, 28 (25%) Ewing's Family Tumors, 1 (1%) adamantinoma. Neoplasms were located in the femur in 67 patients (60%), the tibia in 30 (27%), and the humerus in 14 (13%).

Femoral reconstruction utilized megaprotheses in 41 cases (61%) and MBA in 20 (30%), while in 6 children (9%) the combination of MBA and conventional prosthetic components (Allograft-Prosthesis-Composite, APC) was used. The tibia was reconstructed in 15 patients with MBA (50%), 10 cases with APC (33%), and 5 patients with megaprotheses (17%). In 17 cases of intercalary reconstructions of the lower limb (8 femurs and 9 tibias) MBA was used in conjunction with a vascularized fibula graft (VFG). The humerus was reconstructed with APC in 5 cases (36%), modular prostheses in 3 (21%), MBA in 3 (21%) and with VFG alone in 3 (21 %).

In summary, 49 skeletally immature patients (44%) had the limb reconstruction obtained by a megaprosthesis; in 59 children (53%) a MBA was used : alone in 21 cases, with VFG in 17, and with standard prosthetic components in 21. VFG alone was used in the last 3 cases

No allograft related disease was observed.

Postoperative deep infection occurred in 4 patients reconstructed by megaprotheses (8%) , in 1 case with APC (5%) but no septic complication was noted in intercalary or osteoarticular MBAs and in VFG reconstructions..

**Conclusions:** MBAs allow custom reconstructions with unique biologic and biomechanic properties, particularly helpful in restoring the bone stock lost in growing patients due to tumor resection. In bone reconstructions, the use of MBA do not increase the risk of postoperative infection and may be biologically augmented with vascularized autografts Tissue banking allows for access to a greater number of reconstructive options, often at a significantly lower cost than mega- prosthetic counterparts. In this series, more than half of the limb salvage procedures in children involved the use of MBA from our CMSTB, evidence of the safe strong role that bone banking can play in limb-sparing reconstruction of young oncologic patients.

# LONG TERM OUTCOMES FOLLOWING ENDOPROSTHETIC REPLACEMENTS

003

H. Wafa, R.J. Grimer, M.S. Bartoli, S.R. Carter, R.M. Tillman, A. Abudu, L. Jeys

The Royal Orthopaedic Hospital Oncology Service, Birmingham, United Kingdom.

Corresponding author: Hazem Wafa email: hazem.wafa@nhs.net

**Objectives:** To establish what happens to patients in the long term (>20 years) following endoprosthetic replacement.

**Introduction:** Limb salvage surgery had replaced amputation as the preferred treatment modality in more than 90% of the patients with extremity sarcomas. Endoprosthetic reconstruction has the advantage of providing immediate stability, thus allowing early mobilization, rehabilitation, and weight bearing. However, the long term results of these megaprotheses are still lacking.

**Methods:** A prospective database contains details of all patients treated at our unit with musculoskeletal tumours. All patients who underwent an endoprosthetic replacement more than 20 years ago (prior to 31/12/1990) and who were still alive were identified and their outcomes investigated with particular reference to the development of complications and the need for further surgery. 231 patients who had complete follow up and were alive at 1/1/2011 were identified. The mean age at diagnosis was 20.8 years (range, 5-62 years). The most common diagnoses were osteosarcoma (132) followed by Ewing's sarcoma (31) and chondrosarcoma (23). There were 102 distal femoral, 60 proximal tibial, 26 proximal femoral, 20 proximal humeral, 8 intercalary, 5 total femoral, 5 total humeral, 4 hemipelvic, and 1 distal humeral endoprosthetic replacements.

**Results:** All patients were followed up for a mean period of 23.1 years (range, 20 to 40.1 years). The 231 patients had a total of 612 further operations (excluding lengthening of expandable prostheses). This averaged 2.4 further operations per patient over a minimum of 20 years. The risk of amputation was 12% at 20 years and 15% at 30 years in this group. Of the 31 patients who had an amputation, 18 were due to infection and 9 due to local recurrence. Only one patient had an above knee amputation for fixed flexion deformity of the knee while none of the amputations were done purely for mechanical failure.

The risk of infection persisted throughout the life of the prosthesis and averaged about 1% per year. Of the 60 patients who developed an infection, only 11 developed it within 6 months of a previous surgery – suggesting that the risk of infection following any further surgery was around 2%. The biggest risk sites for infection were the proximal tibia (43.3%), proximal femur (26.9%) and the distal femur (22.5%) and for amputation were the proximal tibia (26.7%) and the proximal femur (15.4%).

MSTS functional scores were calculated on all patients with an existing prosthesis. A hundred and eighty-eight patients (94%) had excellent or good results (MSTS score of 15-30), while the remaining twelve patients (6%) had fair or poor results (MSTS score of 0-14).

**Conclusions:** Endoprosthetic replacement is a valid reconstructive technique in limb salvage surgery with satisfactory long term results. Patients should be warned of the likelihood for the need for revision surgeries. The life-long potential risks of infection and amputation should also be considered.

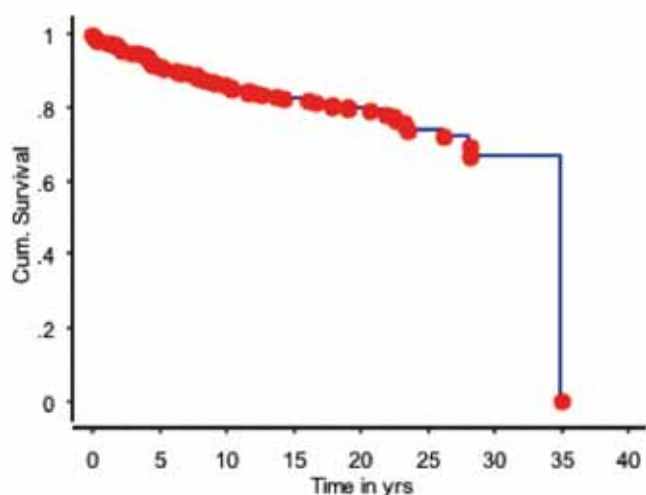


Fig. 1 Risk of infection after endoprosthetic replacement

# PROXIMAL TIBIAL MEGAPROSTHESES AFTER RESECTION FOR BONE TUMOR: SURVIVAL OF THE IMPLANTS AND FUNCTIONAL RESULTS

046

Elisa Pala, MD; Andrea Ferraro, MD; Gabriele Drago, MD; Matteo Romantini, MD; Andreas F. Mavrogenis, MD; Douglas Letson, MD, PhD; Pietro Ruggieri, MD, PhD;

IV Department of Orthopaedics, University of Bologna, Istituto Ortopedico Rizzoli, Bologna, Italy

Sarcoma Program, H. Lee Moffitt Cancer and Research Institute, Tampa, Florida, USA.

**Objectives:** Previous studies reported variable outcome and complications rates after proximal tibial resections and different types of megaprosthesis and extensor mechanism reconstructions. Therefore, we performed this study to evaluate the survival, Musculoskeletal Tumor Society (MSTS) function and complications of the patients, the megaprosthesis and the extensor mechanism reconstructions in this location.

**Material and Methods:** We retrospectively studied the files of 225 patients with tumors of the proximal tibia treated at our institution with proximal tibial resection, megaprosthesis and extensor mechanism reconstruction from March 1985 to August 2010.

Reconstruction of the extensor mechanism and wound coverage was performed with the present technique: direct attachment of the extensor mechanism to the megaprosthesis with non-absorbable sutures, mechanical clamping with a polyethylene plate, or an artificial ligament, with or without a gastrocnemius muscle flap in 58 cases, LARS® artificial ligament in 7 cases, Leeds-Keio® artificial ligament in 2 cases, equine pericardium xenograft in 3 cases, gastrocnemius muscle flap and non-absorbable sutures inserted through the anterior holes of the prosthesis in 167 cases.

The mean follow up was 7 years (median, 56; range, 2-294). The survival, MSTS function, and complications of the patients and the megaprosthesis and extensor mechanism reconstructions were analyzed.

**Results:** Survival of the patients with sarcomas was 68% and 62% at 5 and 10 years. Survival of the megaprosthesis reconstructions was 82% and 78% at 5 and 10 years, without any difference between fixed and rotating hinge megaprotheses. At univariate and multivariate analysis, the only predictor of MSTS function was the type of hinge. The mean MSTS functional score of patients was 77% (range, 27% to 100%). MSTS function was statistically significantly better for patients with rotating hinge megaprotheses ( $p=0.042$ , Kruskal-Wallis test). MSTS function in the different types of extensor mechanism reconstructions was not significantly different. Overall complications rate was 25%: infection (12%), aseptic loosening (6%), and this rupture of the extensor mechanism (3%). According to Letson et al. classification of failures these were classified as: type I 3%; type II 6%, type IV 12%.

**Conclusions:** The type of hinge was the only univariate and multivariate factor statistically influencing function of patients with proximal tibial resections and reconstructions. Patients with rotating hinge megaprosthesis reconstructions have better function regardless of the type of extensor mechanism reconstruction. Overall survival of the implants was satisfactory.



## FUNCTIONAL RECONSTRUCTION AROUND THE KNEE WITH MEGAPROSTHESIS

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*Domenico A. Campanacci, Giuseppe Caff, Filippo Frenos, Sarah Chacon, Nicola Mondanelli, Giovanni Beltrami, Guido Scozzianti, Rodolfo Capanna*

*Department of Orthopaedic Oncology, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy*

**Objective:** Extensive bone loss around the knee may be due to bone tumor resections, conventional prostheses failure and postraumatic sequelae. Distal femoral and proximal tibial defects can be effectively reconstructed by modular prostheses but in selected cases the use of an allograft-prosthesis composite (APC) may provide a functional advantage. The objective of the present study was to review our series of functional prosthetic reconstructions around the knee (with and without allograft) with the aim to evaluate morbidity and implant survival.

**Materials and Methods:** From 2001, 194 patients (90 F, 103 M) were treated at authors' Institution with modular prosthetic reconstruction of the knee joint after resection of a malignant bone tumor in 142 cases, benign bone tumor in 36 cases and in bone loss due to non oncologic conditions in 16 cases. Megasystem C, Waldemar Link, was used in all reconstructions. A distal femur prosthesis was implanted in 135 cases (in one case a distal femur prosthesis was associated to an APC of proximal tibia) while a proximal tibia reconstruction was performed in 45 cases. Proximal tibial replacement was done with modular prosthesis in 23 cases and with APC in 22 cases. In 14 cases, due to the extension of the tumour into the joint space, an extra-articular resection was performed, with functional reconstruction by an APC with complete allogenic extensor apparatus.

**Results:** At an average follow up of 30 months, 54 major complications in 35 patients (18%) were observed and 44 prosthetic surgical revision were performed. Deep infection was observed in 20 cases (10.3%). Eighteen prosthetic mechanical complications were seen (morse taper failure in 11 cases, articular joint failure in 5 cases, disassembling in 2 cases). An aseptic loosening occurred in 2 cases requiring surgical revision with a total femur prosthesis in 1 case. Two patients developed a wound dehiscence treated with a rotational flap. A patellar tendon detachment was seen in 7 cases, requiring surgical revision in 5 cases. Two traumatic patella's fractures and 1 traumatic periprosthetic fracture were observed. A local recurrence occurred in 12 cases and surgical treatment was an amputation in 6 cases. Among the evaluable patients with at least a 12 months follow up, 72% showed satisfactory functional results (excellent or good following MSTs functional evaluation).

**Conclusions:** In our experience, Megasystem C showed to be an effective tool in articular reconstruction of segmental bone loss around the knee. The conventional modular assembling was the preferred choice in distal femur. In proximal tibia reconstructions, conventional modular implants showed a higher incidence of infections and lower functional score than APC assembling. After extra-articular knee resections, an effective functional reconstruction was achieved combining the conventional modular assembling of distal femur to an APC of the proximal tibia with allogenic extensor apparatus.

# COMPLICATIONS AND FUNCTIONAL OUTCOME AFTER RECONSTRUCTION OF THE KNEE EXTENSOR MECHANISM USING A LARS®-LIGAMENT FOR MUSCULOSKELETAL TUMORS

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GM. Hobusch, C. Hourscht, M. Dominkus, R. Windhager, PT. Funovics

Department of Orthopaedic Surgery - Medical University of Vienna – Austria

**Objectives:** The aim of this retrospective, single centre study was to examine functional results and complications in patients undergoing reconstruction of the knee extensor mechanism using a LARS®-ligament after musculoskeletal tumour resection and endoprosthetic reconstruction.

**Material and Methods:** The study cohort comprised 56 patients (32 men and 24 women; mean age, 29 years; range 12-86 years) with a minimum follow-up of 24 months (mean, 57 months; range, 24-117 months). Data was retrospectively retrieved from the prospective Vienna Bone and Soft Tissue Tumour Registry and patient files. Indications for tumor resections were 34 osteosarcomas, 5 chondrosarcomas, 3 ewingsarcomas, 5 leiomyosarcomas, 2 synovialsarcoma, 1 myxofibrosarcoma, 1 histocytoma, 2 giantcelltumor, 1 plasmocytoma and one metastasis. Endoprosthetic reconstructions included proximal tibia reconstructions in 26 patients, distal femur reconstructions in 17 patients, combined proximal tibia and distal femur reconstructions in 12 and one total femur reconstruction. 40 patients received the LARS®-ligament during index surgery, 16 patients had the ligament implanted during a revision of their prostheses. Complications were analysed according to the classification of Hendersen et al. as soft tissue failures (Type I), aseptic loosening (Type II), structural failures (Type III), infection (Type IV) and tumour progression (Type V).

**Results:** At latest follow-up, the mean active ROM in flexion was 97° (SD ± 21°) with a lack of extension of 20° (SD ± 26°). In patients with primary implantation of the LARS®-ligament, soft tissue failures occurred in 18%, aseptic loosening in 10% and structural failures in 15% of the cases. In patients with secondary ligament implantation respective rates were 10%, 18% and 18%. The infection rate in primary implantations of the LARS®-ligament was 26%, however, this rate rose to 45% when the LARS®-implant was used in the course of a revision operation. Local tumour progression was observed in 6% of primary implantations and 5% of the revision patients.

**Conclusion:** The LARS®-ligament offers the possibility of excellent extensor system reconstruction in primary implantation. In the case of repeated revisions the secondary use of the implant is to be indicated very restrictively due to the potential risk of consecutive infection.

## CUSTOM IMPLANTS FOR PRIMARY AND REVISION LIMB SALVAGE SURGERY IN MUSCULOSKELETAL ONCOLOGY

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N. FABBRI, M. Manfrini, P. Unwin, P. Ruggieri

<sup>1</sup> Istituto Ortopedico Rizzoli, Bologna, ITALY

**Objectives:** While representing the only available option in the beginning of the limb salvage era of musculoskeletal oncology, custom made implants have been falling out of favor in many centers with the advent of modular “off the shelf” massive implants. However, there seems to be currently a resurgence and renovated interest for custom implants to address specific and often challenging patient-related issues, such as marked bone loss, unfavorable geometry, poor bone biology, and skeletal immaturity. Goal of this paper is to review and analyse indications and results of treatment in a selected group of patients managed by a custom made implant to address different clinical needs.

**Materials e Methods:** It is a retrospective study of 11 patients; indication to a custom made implant was due to skeletal immaturity in 7 patients (all 7 noninvasive distal femur extendible implant), mainly to bone loss in 2 patients (one distal tibia segmental defect, one failed DF extendible with well-fixed femoral stem), to bone loss and skeletal immaturity in one patient (one failed DF extendible with well-fixed femoral stem), and to a difficult geometry in the remaining patient (low-grade chondrosarcoma of the glenoid region of the scapula). It seems that the indication to a custom implant is often multi-factorial. There has been no implant failure in this series other than 1 local recurrence in a DF extendible.

**Results:** Implant was available within 4 weeks from the formal implant order. Costs have been considered comparable to alternative reconstructive options. The custom implant is functional at latest follow-up in all the patients who remained continuously disease-free.

**Conclusions:** The use of custom made implants is currently increasing when compared to 10-20 years ago and it appears related to improved manufacturing efficiency, faster delivery and satisfactory clinical results.

Murat Hiz, Atakan Karabiber, Hüseyin Botanlioğlu, Fatih Kantarcı, Sergülan Dervisoğlu

Departments of Orthopaedics and Traumatology, Radiology, Pathology, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey

**Objectives:** Intraarticular soft tissue tumours of the knee joint create some particular problems regarding to obtain accurate histopathological diagnosis prior to definitive surgery. Even though most of these tumours are benign in nature, highly malignant tumours such as synovial sarcoma should be kept in mind before biopsy. Arthroscopic or cutting needle core biopsy yield to intraarticular contamination necessitating extraarticular resection of the knee joint. Open frozen biopsy during surgery with a thorough investigation of the knee joint with gadolinium enhanced MRI prior to operation could be an effective strategy to avoid catastrophic contamination of the joint space by other means of biopsy.

**Materials and methods:** 19 patient with intraarticular soft tissue tumours were treated with open frozen biopsy and resection by the senior author in last two decades. 10 female 9 male with a mean age of 38,78 (min 19, max 58 years). All patients had a history of swelling of the knee joint, restriction of active knee extension and moderate pain during stair climbing. All patients investigated by plain X-rays and gadolinium enhanced MRI prior to operation 11 patients had giant cell tumour of the tendon sheaths, 1 patient had juxtaarticular chondroma, 6 had synovial sarcoma, 1 patient had fibrosarcoma. Ill defined borders, invasion of the joint capsule, presence of necrosis in the mass and marked gadolinium enhancement on MRI predicted malignant tumour. Presence of blood stained joint fluid during frozen biopsy was also a marked diagnostic feature of synovial sarcoma. Adjacent bony invasion was present in 3 giant cell tumour of the tendon sheath patients. Frozen biopsy was successful enough to distinct malignant tumours from benign tumours. Permanent sections of the resected specimens revealed no false positive or false negative results. All patients had resection with tumour free margin. Hoffa Fat pad, synovium and joint capsule were removed when indicated. Capsular repair was performed by prolene mesh in 4 patients with synovial sarcoma. Vacuum suction drains were removed 24 hours after the operation. An adjustable knee brace was used for 6 weeks in the patients who required capsular repair. 3 patients required local fasciocutaneous rotational flaps to cover the prolene mesh.

**Results:** At 74 months mean follow up, 1 patient with synovial sarcoma developed local recurrence and converted to extraarticular resection and fixed hinge tumour resection prosthesis. All synovial sarcoma patients received 50 Gys irradiation postoperatively. 6 Patients also received chemotherapy. Oncological results in malignant tumours were: 2 patient died of disease, 5 patients showed no evidence of disease. No benign tumours recurred yet. 3 benign tumour patients had cementation of bony defects. Functionally all patient regained full ROM and weight bearing at 3. months.

**Conclusions:** Intraarticular soft tissue masses should be examined thoroughly before surgical removal. Arthroscopic biopsy or removal of these tumours by shavers without any histological diagnosis or leakage of malignant tumours to the joint cavity after cutting needle core biopsy would result with intraarticular contamination leading to extraarticular resection and prosthetic reconstruction. Open frozen biopsy during definitive surgery with clear margin is a reasonable strategy in such conditions.

## RESULTS OF USING OF GROWING ENDOPROSTHESIS OF HIP JOINT WITH DOUBLE CUP IN THE CHILDREN WITH BONE SARCOMAS

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A.Z. Dzampaev, D.B. Khestanov, D.V. Nisichenko, N.M. Ivanova, M.D. Aliev

**Purpose:** To investigate results of using of growing endoprosthesis of hip joint with double cup in children with bone sarcomas.

**Materials and methods:** In the Institute of Pediatric Oncology and Hematology Russian Cancer Research Center from 2006 to present days were implanted 31 growing endoprosthesis with double cup. The age of patients are ranged from 5 to 15 years. In 16 cases were implanted total endoprosthesis of femur, in 12 — proximal femur and in 3 cases was performed revision procedure. In all cases were implanted double cup D38-D46. We use endoprosthesis LINK, Implantcast (MUTARS) and WRIGTH. Elongation procedures were microinvasiv for LINK type or non-invasive for other types of endoprosthesis.

**Results:** The prostheses were lengthened by a mean of 15 mm (5 to 20). The mean Musculoskeletal Tumour Society score was 80%. We not observed no one cases of dislocation in hip joint, deformation of acetabular or local osteoporosis.

**Conclusion:** The early results from patients treated with this device have been encouraging. The use of endoprosthesis of hip joint with double cup are less invasive and provide good functionally results.

S. Fuchs-Winkelmann<sup>(1)</sup>, B. El-Zayat<sup>(1)</sup>, T. Heyse<sup>(1)</sup>, N. Fanciullacci<sup>(2)</sup>, Y. Chevalier<sup>(3)</sup>, B. Innocenti<sup>(3)</sup>

<sup>(1)</sup> Department of Orthopaedics, University Hospital Marburg, Marburg, Germany

<sup>(2)</sup> Department of Mechanics and Industrial Technology, University of Florence, Florence, Italy

<sup>(3)</sup> European Centre for Knee Research, Smith&Nephew, Leuven, Belgium

**Objective:** To improve component stability in hinged Total Knee Arthroplasty (TKA), different stem lengths could be included during surgery. The stem, which can be either cemented or uncemented, transfers stress from the damaged proximal bone surface to the distal cortical bone. However, no evidence-based guidelines are available to help surgeons decide on the length of stem and whether to cement it or not. A numerical model was developed to compare different fixation techniques and stem lengths in a hinged TKA during a lunge and a squat.

**Methods:** A physiological 3D tibia model was created from Computed Tomography images of a left mechanical-equivalent Sawbone tibia. A hinged TKA (RT-PLUS, Smith&Nephew, Memphis, TN) was selected for the study. Four different configurations were considered: a short cementless stem, a long cementless stem, a short cemented stem and a long cemented stem. The short and long stems had a length of 95 and 160 mm respectively. Stem lengths and sizes were selected based on experimental tests. Loading conditions for squat and lunge motions were calculated using a validated musculoskeletal model and were applied in the finite element model. For all the movements and configurations stresses in selected regions of interest and micromotions between the implant and the bone were computed and compared.

**Results:** Figures 1 illustrates the distribution of the average compressive stress for the four analyzed configurations in the squat movements as a function of the distance from the tibial cut. For both movements, the most stressed regions were situated around the stem tips and the presence of cement reduced the stresses along the bone-cement interface compared to the cementless configuration. The maximal average compressive stress was higher for the cementless long stem configuration (squat 18.2 MPa, lunge 17.7 MPa) and lower for the cemented long stem configurations (squat 11.5 MPa, lunge 10.1 MPa). Also, for the short stem, the cementless configuration showed a higher average compressive stress (squat 13.3 MPa, lunge 14.6 MPa) compared to the cemented configuration (squat 9.5 MPa, lunge 10.4 MPa) in the region situated around the stem tips. However, cemented and cementless short stems showed similar maximal stresses in a region below the stem tip. Cementless stems show higher micromotions compared to cemented stems (~50%) . Long cemented stems result in lower micromotions (~50  $\mu$ m) compared to short cementless stems (~120  $\mu$ m).

**Conclusions:** The presence of cemented stem induces lower stresses in the tibial bone-stem interface and lower micromotions between implant and bone compared to cementless stem. A short stem shows similar maximal stresses in a region below the stem tip.

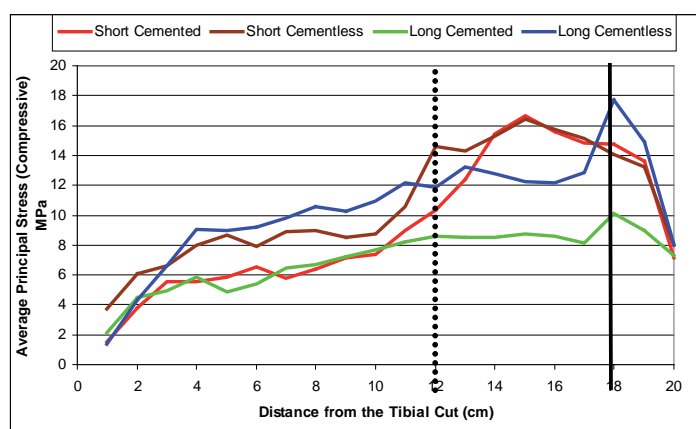


Figure 1: Average principal stress (Compressive) in the 20 region of interest analyzed during the lunge. The two vertical black lines in the figures represent the region of interest corresponding to the short stem tip (dotted line) and to the long stem tip (continuous line).



# THE FIRST NON-INVASIVE JOINT-SPARING GROWING PROSTHESIS WORLD-WIDE FOR AN OSTEOSARCOMA OF THE PROXIMAL TIBIA

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K.Modaressi, B.Fuchs

University Hospital Balgrist, Orthopedic Research, Forchstrasse 340, 8008 Zürich

**Introduction:** Malignant bone sarcomas of the growing skeleton represent a particular challenge. Amputation is very mutilating, and rotationplasty although functionally a good alternative, is not opted for because of its disfiguring aspect. A growing prosthesis may represent an alternative, particularly when there is considerable growth left. Further, sparing the joint may offer great functional advantages whereas –in contrast to resecting the joint- a closer margin must be accepted. We herein represent the world-wide first non-invasive joint sparing growing prosthesis which was implanted in a 10 year old child.

**Results/Case Report:** A 10 year old male represented with pain in the proximal tibia after a fall. A non-displaced pathological fracture at the proximal tibia was seen, and a biopsy revealed an osteosarcoma. The boy underwent neoadjuvant chemotherapy according to the EURAMOS protocol, and then resection of the proximal tibia sparing the epiphysis was performed. A custom made growing prosthesis (Stanmore Implants) was manufactured. This uncemented HA-coated growing prosthesis has a plateau which receives the remaining epiphysis (of ca 1cm thickness) and which allows the fixation of the tibial plateau with screws. The extensor mechanism was reconstructed using a medial gastrocnemius flap together with a split skin graft. The soft tissues healed uneventfully, and adjuvant chemotherapy was resumed 3 weeks postoperatively. Six months later, the prosthesis was non-invasively lengthened using an external magnet. The patient has full extension and walks without walking aids.

**Conclusions:** A non-invasive joint sparing growing prosthesis represents a valuable alternative for young children with bone sarcomas. Although technically certainly challenging, it leads to good function, and the non-invasive growing can be performed on an outpatient basis. However, the costs are high.

G. Gradl, C. Kirchhoff, L. Postl, H. Rechl, R. v. Eisenhart-Rothe

Klinik für Orthopädie und Unfallchirurgie, Klinikum Rechts der Isar, Technische Universität München

Corresponding author:

Guntmar Gradl

Klinik für Orthopädie und Sportorthopädie,

Klinikum Rechts der Isar, Technische Universität München

email: guntmar.gradl@mri.tum.de

**Introduction:** Malignancies of the lower extremity can have a devastating effect on the patients' mental status and quality of life after treatment. Recently, due to significant advances in modern megaprotheses, amputation and rotationplasty seem to have lost some of their importance. Rotationplasty has proved to be an effective, highly functional option in treating malignant tumors of the femur. Therefore the aim of this study was to assess long term results of rotationplasty, compare it to known alternative options of treatment and to evaluate the psychosocial impact.

**Material & Methods:** 23 patients who underwent rotationplasty at our University Department of Orthopaedics between the years 1991 and 2001 were contacted. Twelve out of these 23 patients were enrolled in the study. After a physical examination they were evaluated regarding function of the affected extremity and their psychosocial status. The long term outcome was assessed using the Tegner-Activity score, the SF-36 test and the musculoskeletal society tumor score (MSTS).

**Results:** Average follow up for the 12 enrolled patients was  $14 \pm 3$  years. Average age at the time of surgery was  $19 \pm 10$  years and  $32 \pm 11$  years at the time of follow up. The Tegner score resulted in  $4.1 (\pm 0.6)$ , the average MSTS accounted for  $64\% (\pm 12\%)$ . The results of the SF-36 were  $46.6 (\pm 8.3)$  in the Physical Component Summary Scale and  $58.9 (\pm 5.5)$  in the Mental Component Summary Scale.

**Conclusion:** In comparison with the outcome data available for alternative treatment options in malignancies of the lower extremity, rotationplasty is viable alternative, leaving the patient with relatively high levels of health-related quality of life and function as well as a high degree of social integration.

**Keywords:** malignant bone tumor, distal femur, rotationplasty, outcome, function, quality of life

# PERIPHERAL NERVE RECONSTRUCTION IN LIMB SALVAGE SURGERY - EXPERIENCES FROM THE VIENNA BONE AND SOFT TISSUE TUMOR REGISTRY

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V. Stockhammer, T. Tiefenböck, J. Panotopoulos, M. Dominkus, R. Windhager, P. T. Funovics

Departement of Orthopaedics, Medical University of Vienna, Austria

**Objectives:** The surgical treatment of malignant musculoskeletal tumors requires wide resection. In case of entrapment of peripheral nerves, resection of these structures may become inevitable and can require segmental reconstruction by use of transplants. Reports on the outcomes of peripheral nerve reconstruction after sarcoma resection, however, are sparse.

**Material and methods:** We therefore evaluated prospectively collected data of the Vienna Bone and Soft Tissue Registry of patients who underwent wide sarcoma resection of the extremities accompanied by nerve resection and reconstruction. Twenty-nine patients (13 men, 16 women; mean age 35 years; range, 6-79 years; mean follow up, 89 months; range, 2-272 months) underwent tumor resection and segmental nerve reconstruction, including 11 bone sarcomas (osteosarcoma, 6; Ewing's sarcoma, 2; chondrosarcoma, 2; hemangioendothelioma, 1) and 18 soft tissue tumors (synovial sarcoma, 6; peripheral nerve sheath tumor, 6; myxofibrosarcoma, 2; pleomorphic sarcoma, 2; liposarcoma, 1; leiomyosarcoma, 1). Sixteen out of 29 patients had precedent surgery outside our institution: 8 patients had previous inadequate resections, 6 patients had open biopsies, and 2 patients had local recurrence after initial adequate resection. One patient received neo-adjuvant radiation and 9 patients had neo-adjuvant chemotherapy.

**Results:** Tumor resections included 22 tumor resections - 3 of them with endoprosthetic reconstruction (1 total humerus, 1 proximal humerus, 1 proximal femur) - 6 resection-replantations of the upper extremity, and 1 rotation plasty of the hip with saddle prosthesis. Seven patients had more than one nerve reconstruction. For these, 23 sural autologous nerve grafts and 15 reconstructions without a transplant were used. Reconstructions included the peroneal nerve in 9, the ulnar nerve in 7, the radial nerve in 6, the median nerve in 6, the femoral nerve in 2, the sciatic nerve in 2, the tibial, musculocutaneous, suprascapularis and C6 nerve root in 1 case, each. The average sural graft length was 14cm (range, 5-23cm). Additional reconstructive procedures included 8 vascular reconstructions, 6 muscle flaps and 5 mesh skin grafts. Secondary reconstructive procedures were performed in 5 patients. Fifteen patients received post-operative radiation and 29 had chemotherapy. The grade of postoperative muscle strength for the re-innervated muscle groups was available in 18 patients with a mean of M3 (M0 - M4). Seven patients developed complications requiring revision surgery, including 2 soft tissue break-downs, 2 mechanical failures, 1 arterial spasm, 1 neuroma, and 1 infection. Patients with sural nerve autografts did not complain about pain or discomfort at the donor site. Local recurrence occurred in 4 patients after a mean of 45 months and 6 patients developed metastases after a mean of 28 months. The 5 year survival rate of all patients was 76 percent.

**Conclusion:** Nerval reconstruction is a most valuable method in limb salvage surgery, providing partial restoration of function in most of the patients and a low complication rate.

Schmidt R., Sperk E., Reis T., Bludau F., Wenz F., Obertacke U.

<sup>1</sup>Department of Orthopedics and Traumatology, University Medical Center Mannheim, Germany

<sup>2</sup>Department of Radiation Oncology, University Medical Center Mannheim, Germany

**Objectives:** The new technique of combined kyphoplasty and intraoperative radiation (Kypho-IORT) has shown its clinical feasibility and short term safety which allowed further evaluation of the technique. However, theoretically Kypho-IORT could also enable higher local radiation doses due to the steep dose fall off of the radiation source. Intermediate prospective follow-up can give first information especially by the rate of local tumor control. Therefore we present the first 9 months follow-up after Kypho-IORT.

**Materials and Methods:** All patients who underwent Kypho-IORT and finished the 4<sup>th</sup> follow-up appointment after around 9 month were included. Acquired basic data were gender, age at surgery, tumor entity, treated vertebral level. Prospective collected data were pain measure by visual analogue scale (VAS) preoperative and at follow-up, Karnofsky Index, local metastasis control in the treated vertebra and general progression of metastases by CT or MRI.

**Results:** 8 patients (5 females, 3 males) with an average age of 60 years were included. 4 patients had breast cancer and one each with prostate, lung, ovarian and sigmoid cancer. 9 vertebrae from Th5 to L1 were treated with an average surgical time of 83 minutes. The time from surgery to latest follow-up was in average 293 days. The Karnofsky index was constant with 88 preoperative versus 86 at follow-up. The VAS average decreased from 5 preoperative to 2 postoperative and 1.5 at final follow-up. 1 patient had a local progress which needed open revision surgery, whereas 4 had a general tumor progress. No secondary fractures of the treated vertebrae occurred.

**Conclusions:** Kypho-IORT can lead to fast postoperative pain reduction, immediate stabilization and prevention of secondary fractures in the treated vertebra by kyphoplasty which could be confirmed in this small cohort. VAS decreased postoperative and this level was maintained during follow-up. Local tumor control by intraoperative radiation could be achieved in 87% over the 9 months period, which seems to be better than single fraction radiation schedules and at least comparable to multiple fraction schedules of conventional radiation. These results warrant further evaluation of this technique by a dose escalation and a multicenter study, which is currently under way.

## PREOPERATIVE CHEMO-RADIATION THERAPY MAY OFFSET THE NEGATIVE PROGNOSTIC IMPACT OF CLOSE/POSITIVE SURGICAL MARGINS ON OUTCOME: AN EXPLORATORY ANALYSIS FROM A PHASE III RANDOMIZED TRIAL BY ITALIAN SARCOMA GROUP AND SPANISH SARCOMA GROUP.

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Alessandro Gronchi, Paolo Verderio, Andrea Ferraro, Vittorio Quagliuolo, Antonino De Paoli, Claudia Sangalli, Javier Martin, Antonio Lopez-Pousa, Franco Gherlinzoni, Piero Picci, and Paolo G. Casali

**Background:** The impact of surgical margins on outcome in soft tissue sarcoma has long been debated. On the one hand some retrospective series on large number of patients have shown a negative impact of positive surgical margins on local and distant recurrence and disease specific survival. On the other hand some other have only found a negative impact on local control, without any effect on distant outcome or survival. Since radiation therapy (RT) and also chemotherapy (CT) have been shown to play a role in local control, we decided to explore the correlation between quality of surgery and outcome in a homogeneous population of high-risk STS treated within a phase III randomized trial by preoperative CT or CT-RT.

**Methods:** Patients were randomized either to receive 3 cycles of preoperative CT with Epirubicin 120 mg/m<sup>2</sup> and Ifosfamide 9 g/m<sup>2</sup> and G-CSF (Arm A) or to receive the same 3 cycles of preoperative CT followed by 2 further cycles of post-operative CT (Arm B). Radiotherapy could be either delivered in the preoperative or in the post-operative setting. Correlation between surgical margins and outcome (overall survival, local recurrence and distant metastases) was studied by multivariable analysis.

**Results:** Between January 2002 and April 2007, 328 patients were recruited, 164 in each arm. 160 patients received preoperative radiation therapy, 78 in Arm A and 82 in Arm B. Median tumor size was 10 cm. Microscopic status of surgical margins was negative in 84.8% of cases, positive in 8.8%, and missing in 6.4% of cases. Primary amputation rate was 8%.

At a median follow-up of 60 months (IQR 47-74 months), 5-year OS was 0.70 for the entire group of patients, 0.69 and 0.71 in arm A and B, respectively. 20 patients developed local recurrence (LR) after surgery (11 in arm A and 9 in arm B) as primary event, while 102 patients developed DM (50 in arm A and 52 in arm B).

Overall cumulative incidence of LR at 5 yrs was 0.062 (SE  $\pm$  0.014), 0.065 (SE  $\pm$  0.020) in arm A and 0.059 (SE  $\pm$  0.019) in arm B. Overall cumulative incidence of DM at 5 yrs was 0.326 (SE  $\pm$  0.027), 0.321 (SE  $\pm$  0.039) in arm A and 0.033 (SE  $\pm$  0.038) in arm B.

On multivariable analysis, positive microscopic margins significantly affected LR (HR 4.23, 95% CI 1.48-12.12), without any impact on DM (HR 0.95, 95% CI 0.46-1.98) and OS (HR 0.96, 95% CI 0.46-2.00)

**Conclusions:** In this setting of high-risk STS treated by neoadjuvant CT or CT-RT, the negative impact of positive margins on outcome seems limited. When close margins can be anticipated on cross sectional imaging, a preoperative therapy may be of help to maximize the chance of cure at a better functional prize.

# RADIATION THERAPY INCREASED LOCAL CONTROL IN SURGERY OF SOFT TISSUE SARCOMAS OF THE EXTREMITIES BUT INCREASED WOUND COMPLICATION RATE

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T. KLUBA, A. MATZ, B. KUNZE, I. IPACH

University of Tübingen, Orthopaedic Surgery, Germany

**Purpose:** As treatment results for soft-tissue sarcoma still have to be improved, treatment intensification is warranted. We performed a retrospective analysis to compare the different treatment options of radiation treatment in the perioperative setting concerning influence of radiation treatment on local control and wound healing complications after soft tissue sarcoma (STS) resections at the extremities.

**Methods and Materials:** Between 1990 and 2010, 406 patients were surgically treated for STS of the extremities at our institution. 142 patients of these were transferred with a local recurrence after primary therapy abroad. 36 patients had to be excluded because of incomplete documentation. The remaining 228 patients (115 f, 113m) were analysed with regard to wound healing complications related to the time of radiation therapy. The mean age at surgery was 56.6 ( $\pm 15.5$ ) years. The indication for radiation therapy was discussed individually in the tumour board considering the different prognostic factors (grade, resection status, size, histology, location). The mean follow-up time was 40 months.

**Results:** Liposarcomas (n=52), NOS (n=41) and myxofibrosarcoma (n=38) were the most common histological entities. The tumors were graded 1 (29%), 2 (31%) and 3 (40%). 90 patients received no radiation therapy (RT), 37 patients neoadjuvant treatment with radiosensitization (ifosfomide) and / or local hyperthermia and 98 patient were treated with adjuvant radiation.

Wound complications with prolonged local treatment were recorded in 18.9% of patients without radiation, 35.1% with neoadjuvant therapy and 31.6 % with adjuvant radiation respectively. Surgical revisions were required in 7 patients (7.8%) without RT, 10 patients (27%) after neoadjuvant and 19 (19.4%) after adjuvant radiation therapy.

**Discussion:** As in previous publications, radiation therapy is a negative prognosticator for wound complications after STS surgery. Our data suggest that radiosensitizing with ifosfamide and / or locoregional hyperthermia in combination with neoadjuvant radiotherapy has a significantly higher complication rate (revision surgeries) in comparison to the adjuvant treatment. This has to be discussed with the patient, bearing in mind the possible functional advantage in the long term.



## HIGH DOSE RATE BRACHYTHERAPY IN THE MULTIMODALITY TREATMENT OF SOFT TISSUE

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Maccauro G<sup>1</sup>, Graci C<sup>1</sup>, Mattiucci GC<sup>2</sup>, Mantini G<sup>2</sup>, Spinelli MS<sup>1</sup>, Perisano C<sup>1</sup>, Di Giacomo G<sup>1</sup>, Valenzi E<sup>1</sup>, Fabbriani C<sup>1</sup>

<sup>1</sup>Department of Orthopaedics and Traumatology, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

<sup>2</sup>Radiation Oncology Service, Bioimages and Radiological Science Department, Catholic University, Rome, Italy

**Objective:** Conservative treatment of soft tissue sarcomas usually required a combination of surgery and External Beam Irradiation, that is considered an useful adjuvant to surgery: in particular Low Dose Rate Brachytherapy is indicated in intermediate and high grade sarcomas and in recurrence to allow additional local dose in areas at risk for local failure.

The aim of this work is to analyze feasibility, methods, advantages and limits of using High Dose Rate (HDR) Brachytherapy Remote After Loading associated to External Radiotherapy, an interesting perspective in the multimodal treatment soft tissue sarcomas.

**Patients and Methods:** At surgical time total irradiation volume is based on preoperative imaging and histotype. The irradiation area is defined by markers. After tumour resection catheters are placed parallel at 1.5 cm of distance perpendicular to the scar. Seven days after surgery catheters will be loaded to avoid the risk of scar problems. The afterloading catheters can remain in situ for several days to allow the feasibility of fractionated perioperative HDR brachytherapy. The fraction size depends on residual disease. After 2 weeks external beam irradiation is administered.

In this paper, we present the results obtained from the application of HDR Brachytherapy, since 2003, at the Institute of Orthopaedics University of the Sacred Heart in the multimodality treatment of soft tissue sarcoma of the limbs. On a total population of 62 cases of patients with soft tissue sarcoma of the limbs, were selected 12 patients for treatment with wide or marginal surgical excision and treatment with brachytherapy (HDR), followed by external beam radiation therapy. All lesions treated were large (>5cm).

**Results:** To date, in our series there was no case of death. In the cases examined did not occur the presence of any distant metastases, except for a case with lung metastases at diagnosis. In two of the cases examined, there were local recurrence of disease after treatment. In both cases, the lesion was a malignant fibrous histiocytoma pleomorphic high grade. We recorded only one case of severe fibrosis. We had no cases of neurotoxicity.

**Conclusion:** The limb-salvage surgery, HDR Brachytherapy and external beam radiotherapy has been shown, in literature and in our study, positive in lesions with high histological grade of malignancy with resection margins positive or marginal. Although in the literature brachytherapy is used in high-grade lesions, we believe that such treatment, having a low rate of major complications, may be indicated even in low-grade lesions that, for large or for their proximity vascular and/or nervous structures, are difficult resectable with wide margins.

# COMPLICATION OF RADIATION THERAPY FOR SOFT TISSUE SARCOMAS: EXPERIENCE OF ORTHOPAEDIC ONCOLOGY DEPARTMENT OF FLORENCE

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Beltrami G., Caff G., Frenos F., Scoccianti G., Matera D., Campanacci D., Capanna R.

Department Orthopaedic Oncology and Reconstructive Surgery, CTO, AOUC, Florence (Italy)

**Introduction:** Radiation therapy (RT) has an essential role in treatment of soft tissue sarcomas (STS) together with surgery and chemotherapy. STS show significant pathological responses to radiation therapy in the form of hyaline fibrosis, necrosis and granulation tissue; despite the regression of the tumor, many side effects involving bone, soft tissue, wound, nerves, vessels, and lymphatic are associated with RT. We reviewed our cases of STS treated in our Center on the last twenty year and subjected to radiation therapy focusing on the eventual complications.

**Materials and Methods:** At Department of Orthopaedic Oncology of CTO - Florence, we have treated, from January 1989 to December 2009, 1055 patients affected by STS of limbs and superficial trunks. All the patients have been operated and followed by the same equip of surgeons, radiotherapist, micro-surgeons and pathologists, everybody practice in soft tissue sarcoma cases.

Adjuvant protocols of RT was associated to surgery in 477 cases (45,2%): 87 were low grade sarcoma and 390 were high grade. Chemotherapy was also associated in 180 (37,7%) patients: 8 low grade and 172 high grade. The RT medium dose was 60 GY (range 50 to 75 GY).

Side effects after Radiation Therapy have been analysed on the overall group and a statistical analysis have been performed. All minor or major complication related to RT were considered and in particular a free event survival curve regarding the two most common complications (fracture and wound dehiscence) have been performed.

**Results:** At an average follow up of 7 years (1-20 yy), 78 complications occurred in the whole group (16,3%): 17 in patients affected by a low grade STS and 61 by an high grade. The most frequent complications were: 17 cases of fractures (21,8%), 27 wound dehiscences (34,6%), 7 necrosis (8,9%) (interesting the bone in 4 cases and the flap in 3 cases ), 6 neuro palsy (7,6%), 4 lymphedemas (5,1%) and 1 major infection. 7 patients were amputated for complication of RT.

**Conclusion:** Even though the important complications' rate, Radiation therapy plays an essential role in treatment of soft tissue sarcoma as well as adjuvant or neo adjuvant to surgery. A multidisciplinary approach composed by specialists with practice is always necessary to select patients affected by a STS for a possible radiation therapy.

# RETROSPECTIVE ANALYSIS OF TREATMENT RELATED TOXICITIES IN EWING SARCOMA PATIENTS RECEIVING RADIO THERAPY IN COMBINATION WITH OR WITHOUT ACTINOMYCIN D

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U. Dirksen<sup>2</sup>, V. Schüttler<sup>2</sup>, S. Amler<sup>1</sup>, A. Ranft<sup>2</sup>, H. Jürgens<sup>2</sup>

<sup>1</sup>Pediatric Hematology and Oncology, University Hospital, Münster, Germany

<sup>2</sup>Institute of Biostatistics and Clinical Research, Westfalian- Wilhelms University of Muenster, Germany

**Background/Objectives:** Actinomycin D (actD) was the first agent described in association with recall dermatitis in 1959 by D`Angio et al.. Recall dermatitis is an inflammatory reaction of previously irradiated skin ranging from sun- burn like redness to desquamating ulcerative lesions. Radiation recall phenomena may not be restricted to the skin but have also been described as affecting the mucosa or lung tissue. Ewing sarcoma patients treated within the EURO-E.W.I.N.G.99 (EE99) trial received multimodal treatment consisting of chemotherapy, radiotherapy and/or surgery. Maintenance chemotherapy in patients with localized disease or with pulmonary metastases only included actD. It was recommended to avoid actD parallel to radiotherapy in order to prevent severe inflammatory reactions. However, in 34 patients treated within the protocol, actD was not paused parallel to or after radiotherapy. We analysed toxicity and outcome in these patients compared to patients who received no actD parallel to radiotherapy in a matched pair analysis.

**Methods:** A total number of 34 Ewing-sarcoma patients (pts) who underwent chemotherapy with actD parallel to radiotherapy were extracted from the EE99 trial database of the German Society of Pediatric Oncology and Hematology. Additionally, we identified the same number of a suitable control cohort without the use of actinomycinD by means of matched pair analyses, to adjust for risk factors age, tumor origin and total dose of radiation. Toxicity was analyzed according to modified CTC toxicity grade scales of the EE99 protocol.

**Results:** Among the patients who received actD (male: 67.7%; female: 32.3%) 20 pts, 58,8% presented with localized disease, 10 pts with pulmonary metastases (R2pulm; 29.4%) and 3 pts with primary mainly skeletal dissemination (R3; 8.8%), in one patient staging information was missing. The control group was distributed as follows: male: 52.9%; female: 47.1%; localized disease (25; 73.5%; pulmonary metastases 8; 23.5%; disseminated disease: 1; 2.9%).

Grade 3 and 4 toxicity was reported in 69 of 693 incidents (10.0%) receiving radiotherapy without actD, and in 70 of 626 incidents (11.2%) receiving radiotherapy and actD. The majority of toxicities were hematological with no difference in both groups (123 cases; about 50% of pts per group; p=0.617). Major differences with a clinical relevant increase of approximately 10% in dichotomous scales were observed in the actD group regarding: granulocytes (with actD: 77.8% vs. without actD: 60.0%; p=0.168) and platelets (40.6% vs. 31.3%; p=0.603). The three year- overall survival was 0.71; SE=0.09 in both groups. Skin toxicities were reported in three pts who received actD parallel to radiotherapy and in two pts in the control group (p= 0.667). Stomatitis and mucositis were reported in one patient each. In none of the pts the mucosa toxicity was related to the radiation field. Reversible liver toxicity with ALT/AST elevation was reported in one patient each in both groups and bilirubin elevation was reported only in the control group. In none of the pts the liver was in the radiation field. Adjusted for risk group (R1/R2loc; R2pulm; R3) the OS risk ratio for actD vs. no actD was 0.78 (95%CI 0.29-2.08).

**Conclusion:** A number of chemotherapeutics have been associated with radiation recall dermatitis. Case reports and small series are published for actD, bleomycin, doxorubicin, edatrexate, etoposide, hydroxyurea, melphalan, paclitaxel, tamoxifen and vinca alkaloids<sup>2</sup>. Our results show no differences in toxicities in pts who received radiotherapy and actD. This may be contributed to more precise techniques in the field of radiotherapy. There may be an individual pharmacogenomic susceptibility to chemo-radiation – induced dermatitis. Further evaluation is required to clarify which agent is a risk and who as an individual person is at risk.

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# EXPRESSION OF CYCLIN D1 AND BETA-CATENIN IN GIANT CELL TUMOR OF BONE AS A POSSIBLE MARKER OF WNT PATHWAY IN TUMORIGENESIS

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J. Sopta\*, N. Lujic\*\*, Z. Vucinic\*\*, D. Ristic\*\*\*, J. Bokun\*\*\*, L. Paripovic\*\*\*, V. Mijucic\*\*\*

\*Institute for Pathology, Faculty of Medicine, University of Belgrade, Serbia

\*\*Institute for Surgical and Orthopedic Diseases "Banjica", Belgrade, Serbia

\*\*\* Institute for Oncology and Radiology, Belgrade, Serbia

**Objectives** stating concisely why the study was conducted

Aberrant activation of the Wnt signaling pathway is known to contribute to tumorigenesis of a wide range of tumors including some mesenchymal proliferations including giant cell tumor of bone (GCTB). The Wnt signaling pathway is regulated by many components such as  $\beta$ -catenin. Recent studies have shown that *cyclin D1* are important target genes induced by  $\beta$ -catenin.

**Materials and Methods:** Representative formalin-fixed, paraffin-embedded materials for immunohistochemical studies (cyclin D1 and  $\beta$ -catenin) were available in 25 primary and recurrent cases of GCTB diagnosed at the Institute of Pathology, Faculty of Medicine. We compared nuclear labeling index (LI) in primary and recurrent tumors.

**Results:** Nuclei of giant cells (GC) were positive for both (cyclin D1 and  $\beta$ -catenin) primary antibodies. Nuclei of stromal cells (SC) showed Immunoreactivity only for  $\beta$ -catenin. Cyclin D1 LI in nuclei of GC (75.9 vs. 80.4%,  $p=0.314$ ) were not higher in recurrent tumors than in primary tumors. In opposite, recurrent tumors showed higher nuclear beta-catenin labeling index (LI) in both cell types: SC (62.8 vs. 43.1%,  $p=0.064$ ) and GC (49.1 vs. 22.5%,  $p=0.087$ ).

**Conclusions:** This study suggested that cyclin D1 immunoreactivity may be a characteristic immunophenotype of GCTB and nuclear beta-catenin staining level might be associated with tumor recurrence in GCTB. According that we postulated that cyclin D1 may be upregulated through an activated Wnt/ $\beta$ -catenin pathway in GCTB.

## DEACETYLASE SIRT1 LINKS TUMOR SUPPRESSIVE NOTCH SIGNALLING TO P53 IN EWING'S SARCOMA

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Jozef Ban<sup>1</sup>, Argyro Fourtouna<sup>1</sup>, Dave N.T. Aryee<sup>1</sup>, Isidro Machado<sup>2</sup>, Max Kauer<sup>1</sup>, Gunhild Jug<sup>1</sup>, Antonio Llombart-Bosch<sup>2</sup>, Heinrich Kovar<sup>1</sup>.

<sup>1</sup>Children's Cancer Research Institute, St. Anna Kinderkrebsforschung, Vienna, Austria, AT-1090; <sup>2</sup> Department of Pathology, University of Valencia, Valencia, Spain

**Objectives:** Besides its important role in organismal development, NOTCH receptor signaling exerts tissue specific proliferative or antiproliferative functions. While the oncogenic role of NOTCH has been extensively investigated due to its constitutive activation in T-cell leukemias and several epithelial cancers, little is known about NOTCH mediated tumor suppression. We have previously reported that in Ewing's sarcoma, a pediatric bone tumor driven by the chimeric ETS oncogene EWS-FLI1, auto-stimulatory NOTCH signaling is suppressed and that reactivation results in p53 and consequently growth inhibitory p21 induction via activation of the NOTCH effector HEY1. This study was performed to identify the mechanism by which HEY1 regulates p53 in Ewing's sarcoma.

**Materials and Methods:** EWS-FLI1 and HEY1 regulated p53 candidate modulators were identified by gene expression profiling, and validated by ectopic overexpression, chemical inhibition, reporter gene assays, and immunohistochemical analyses of primary tumors.

**Results:** We now demonstrate that HEY1-mediated p53 stimulation is accompanied by C-terminal p53 acetylation as a consequence of downregulation of the deacetylase sirtuin 1 (SIRT1). We found that both EWS-FLI1 and HEY1 bind to the SIRT1 promoter with opposite transcriptional consequences. Thus, knockdown of EWS-FLI1 and ectopic HEY1 expression resulted in similar SIRT1 modulation and p53 acetylation which could be reversed by ectopically expressed SIRT1. Immunohistochemical investigation of a large series of diagnostic primary Ewing's sarcoma samples revealed a marked heterogeneity of SIRT1 expression. Of note, tumors with high SIRT1 expression positively correlated with EWS-FLI1 proliferative activation signature suggesting feed-back regulation between EWS-FLI1 and SIRT1. Consistent with these results, treatment of Ewing's sarcoma cells with the sirtuin inhibitor Tenovin 6 resulted in massive cell death.

**Conclusions:** EWS-FLI1 activates SIRT1 expression by suppressing NOTCH signalling. High SIRT1 suppresses p53 and supports EWS-FLI1 proliferation promoting functions. The cytotoxic effect of SIRT1 inhibitor Tenovin 6 suggests SIRT1 as a candidate therapeutic target in Ewing's sarcoma.

**Support:** This study was supported by grants from the Austrian Science Fund (P22328-B09) and the European Commission (EU-FP7 STREP 259348).

# miRNA – DEREGLATION AS A CRITICAL MILESTONE ON THE ROAD TO OSTEOSARCOMA DEVELOPMENT AND METASTASIS?

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Stephanie Zillmer<sup>1,3,§</sup>, Kathrin Poos<sup>2,§</sup>, Daniel Baumhoer<sup>1,9</sup>, Kristian Unger<sup>4</sup>, Michael Rosemann<sup>5</sup>, Michael J. Atkinson<sup>5</sup>, Martin Irmeler<sup>6</sup>, Johannes Beckers<sup>6,7</sup>, Gernot Jundt<sup>9</sup>, Eberhard Korsching<sup>2#</sup>, Jan Smida<sup>1,8#</sup> and Michaela Nathrath<sup>1,3,8#</sup>

<sup>1</sup>Clinical Cooperation Group Osteosarcoma, Helmholtz Zentrum Muenchen- National Research Centre for Environment and Health, Germany,

<sup>2</sup>Institute of Bioinformatics, Westfälische-Wilhelms Universität Münster, Münster, Germany

<sup>3</sup>Department of Pediatric Oncology, Klinikum Kassel, Germany, <sup>4</sup>Research Unit of Radiation Cytogenetics, Helmholtz Zentrum Muenchen - National Research Centre for Environment and Health, Germany; <sup>5</sup>Institute of Radiation Biology, Helmholtz Zentrum Muenchen- National Research Centre for Environment and Health, Germany; <sup>6</sup>Institute of Experimental Genetics, Helmholtz Zentrum Muenchen- National Research Centre for Environment and Health, Germany; <sup>7</sup>Chair of Experimental Genetics, Technische Universitaet Muenchen, Centre of Life and Food Science Weihenstephan, Germany; <sup>8</sup>Department of Pediatrics, Technische Universitaet Muenchen and Pediatric Oncology Center, Germany

<sup>9</sup>Bone Tumor Reference Center at the Institute of Pathology, University Hospital Basel, Switzerland

<sup>§</sup> The authors contributed equally to this work # Shared senior authorship

Corresponding author: Stephanie Zillmer, Department of Pediatric Oncology, Klinikum Kassel, Germany; Phone: +49-17620326245, Fax: +49-561-9806851, E-Mail: stephie.zillmer@gmx.de

Although comprehensive studies have demonstrated the complex pattern of chromosomal and molecular changes in osteosarcoma, the mechanisms finally leading to osteosarcoma development are not completely understood.

MicroRNA-expression profiling has been established as a method to unravel the impact of miRNA-involvement in malignancies in general. Several studies have been describing deregulated miRNA to affect osteosarcoma pathogenesis, influencing basic pathological cellular processes like cell growth or migration.

Our approach was to examine 6 well-established OS cell lines (MG-63, MNNG/HOS, SJSA-01, SaOS, HOS-58, U2-OS) regarding these biologic processes in vitro, essaying each cell lines' potential to migrate, invade cell membranes and proliferate. Cultured osteoblasts (hFOB 1.19) and mesenchymal stem cells (L87/4) were used for normalization.

Based on their distinct microarray expression patterns, we were able to identify certain miRNA (mir-181a and let7) significantly correlating with the cell lines proliferation, migration and invasion potential, respectively.

By integration of these miRNA expression levels with expression patterns of their target genes we were able to detect biologically active miRNA that seem to function as tumor suppressors or oncogenes in Osteosarcoma.

Our findings indicate that the deregulation of miRNAs play a crucial role in migration and cell growth of osteosarcomas and therefore in their potential to metastasize.

In order to evaluate their functional meaning in vivo we are now starting to analyze the expression profiles of the miRNAs of interest in osteosarcoma biopsy samples.

The goal is to identify candidate miRNA that can be used as biomarkers reflecting the metastatic potential in osteosarcoma.



## CD99 AND P53-ACTIVATING DRUGS IN EWING SARCOMA

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Guerzoni Clara<sup>1,2</sup>, Mario Terracciano<sup>1</sup>, Maria Cristina Manara<sup>1</sup>, Giusy Di Conza<sup>3</sup>, Selena Ventura<sup>1</sup>, Fabiola Moretti<sup>3</sup>, Piero Picci<sup>1</sup> and Katia Scotlandi<sup>1,2,4</sup>.

<sup>1</sup>Laboratorio di Oncologia Sperimentale, Istituto Ortopedico Rizzoli, Bologna, 40136 Italy; <sup>2</sup>Laboratorio PROMETEO, STB, Dipartimento RIT, Istituto Ortopedico Rizzoli, Bologna, 40136 Italy; <sup>3</sup>Institute of Cell Biology and Neurobiology, CNR, Roma 64-00143, Italy; <sup>4</sup>CRS Development of Biomolecular Therapies, Istituto Ortopedico Rizzoli, Bologna, 40136 Italy.

**Objective of the proposed research:** Ewing sarcoma (EWS) is the second most common tumor of bone in pediatric ages. Current therapeutic options involve surgery and highly intensive chemo- and/or radiation therapies frequently associated to relevant short and long term side effects, due to the young age of patients. Identification of new targeted therapies for EWS treatment might improve the cure rate and the side effects arising from employment of chemotherapeutic agents. To identify potential effective targets in EWS treatment we evaluated both monoclonal antibody anti-CD99, which triggers massive and rapid cell death of EWS cells in vitro and in vivo, and small molecules able to activate the p53 oncosuppressor protein.

**Materials and Methods:** To define sensitivity and molecular mechanisms underlying activation of specific signaling pathways after CD99 or p53 triggering we evaluated cell death in a panel of EWS cell lines. Involvement of specific targets was confirmed by western blotting. Combined treatment with chemotherapeutic agents and the p53-MDM2 inhibitor Nutlin-3 was also performed to evaluate potential synergic effects.

**Results:** The monoclonal antibody 0662 is raised against CD99, a transmembrane 32 KDa protein, whose expression is constantly associated to EWS. As pointed out by array studies and subsequent western blotting validations, upon 0662 treatment, the oncosuppressor protein p53 appears to be readily activated by phosphorylation on serine 15, thus resulting in modulation of p53 canonical targets (p21, BAX, cyclin D1, Gadd45 $\alpha$ ). P53 activation is favored by rapid and strong repression of MDM2, an ubiquitin ligase responsible for p53 proteasome dependent degradation. TP53 gene is rarely mutated in EWS and qualifies therefore as potential target. Interestingly, the most CD99-responsive EWS cells have either wild type or transcriptional active P53, though mutated, and greatly benefit from MDM2 degradation. Moreover MDM2 repression may account for increased IGF1R and sustained RAS levels measured after treatment with anti-CD99 antibody. Despite p53 involvement usually commits to cell cycle block or apoptosis, CD99 signaling proceeds without release of cytochrome C from mitochondria and caspase involvement, suggesting that cell death recruits multiple pathways with different outcomes, likely involving sustained RAS activity and massive cytoplasmic hypervacuolization (autophagosomes and micropinosomes). Interestingly, since both p53 and IGF1-R $\beta$  are targeted by the ubiquitin ligase MDM2 for degradation, employment of small molecules inhibiting MDM2 binding and/or activity, may represent another valid therapeutic option. Therefore, we evaluated the efficacy of MDM2 inhibitors such as Nutlin and RITA in Ewing sarcoma cells. Surprisingly RITA is highly effective in reducing growth and tumorigenic potential both in wt-p53 as well as in p53-mutant or truncated Ewing's sarcoma cell lines, suggesting that other targets may be affected by MDM2 regulation. Consistently combined treatment with Nutlin plus conventional chemotherapeutic agents have synergic effects also in p53 truncated cell lines.

**Conclusions:** Due to the low rate of P53 inactivating mutations in EWS patients, these findings sustain p53 and/or CD99-targeting either to directly kill EWS cells or to increase sensitivity to chemotherapy. Small inhibitors affecting MDM2 activity are effective in reducing EWS cell proliferation alone or combined to chemotherapy. CD99, which is easily druggable with monoclonal antibodies, recruits not only p53 but also RAS, thus delivering a signal which exceeds that of drugs designed to reactivate only p53. (grants from Italian Ministry of Health and Italian Association for Cancer Research).

# GIANT CELL TUMOURS OF BONE – CORRELATION OF CLINICAL AND HISTOPATHOLOGICAL FEATURES TO OUTCOME POST-SURGICAL TREATMENT; A SINGLE INSTITUTION EXPERIENCE OF 359 CASES

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L Li<sup>1</sup>, P Chawla<sup>2</sup>, P Gikas<sup>1</sup>, J Jagiello<sup>1</sup>, W Aston<sup>1</sup>, R Pollock<sup>1</sup>, J Skinner<sup>1</sup>, F Amary<sup>1</sup>, T Briggs<sup>1</sup>, A Flanagan<sup>2</sup>

<sup>1</sup> The Sarcoma Unit, Royal National Orthopaedic Hospital, <sup>2</sup> Department of Histopathology, Royal National Orthopaedic Hospital, London, UK.

**Introduction:** Giant cell tumour (GCT) is one of the most controversial and discussed bone tumours. Biological behaviour can be unpredictable and there is currently no consensus as to the best treatment for these theoretically benign lesions. Surgical treatment options include intralesional excision or segmental resection. Curettage has a higher recurrence rate than resection but does preserve adjacent joint function. After curettage, the use of adjuvant therapies is still controversial.

**Aim:** We evaluated (1) clinical and histopathological features of patients with GCT, (2) the recurrence rate and recurrence-free Kaplan-Meier survival function post-resection or curettage, (3) Musculoskeletal Tumour Society (MSTS) functional score (1993 version), and (4) complications after treatment.

**Methods:** We conducted a retrospective review of 359 patients (males and females) with GCT of bone presenting to the Royal National Orthopaedic Hospital to evaluate oncological and functional results.

**Results:** The patients were followed up for at least 12 months. The average age of the patients was 36.9 years (range 1-89 years). Tumours were treated with extensive curettage, local adjuvant therapy (e.g. phenol), cement reconstruction or wide resection +/- use of endoprostheses. The recurrence rates, Kaplan-Meier recurrence-free survival curves, and MSTS functional scores were recorded and correlated to the clinical and histopathological features of these tumours using statistical analysis.

**Conclusion:** This is the largest reported series of giant cell tumours of bone to date and by correlating clinical and histopathological features to outcome post-treatment serves to elucidate the unpredictable behaviour of these tumours, evaluate current surgical treatment options and guide future therapeutic approaches.

# GIANT CELL TUMOR OF BONE: 164 CASES TREATMENT AND OUTCOME FROM SINGLE INSTITUTION

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N. Lujčić\*, J. Sopta\*\*, Z. Vučinić\*, Z. Vukšinić\*, D. Ristić\*\*\*\*, J. Bokun\*\*\*\*G. Tulić\*\*\*

\* Institute for Orthopedic Surgery "Banjica", Belgrade, Serbia

\*\* Institute for Pathology, Faculty of Medicine, University of Belgrade, Serbia

\*\*\* Clinic for orthopedic surgery, University of Belgrade, Clinical centre, Belgrade, Serbia

\*\*\*\* Institute for Oncology and Radiology, Belgrade, Serbia

**Objectives stating concisely why the study was conducted:** The study presents the results of the treatment GCTB over 50 years, specifically, what is the importance of recurrence / residual tumor and its histologic grade, undertaken in relation to the previous operation was performed, justification for certain surgical procedures in relation to the nature of the tumor and finally completes the current treatment protocol algorithm.

**Materials and Methods:** The study is a retrospective analysis for the period 1963-2005 year, used all available documentation Register for Bone Tumors "BANJICA". Histopathologic analysis was performed at the Institute of Pathology, Medical Faculty in Belgrade. The study included 196 patients, treated GCTB. All apatinets were divided into 3 time interval, I group, 1964 – 1983. 76 patients; II group, 1984-1993, 40 patients; III group, 1994-2005, 48 patients.

**Results:** We analyzed the oncologic and functional results, average follow up time was 8.6 years. The average age was  $34 \pm 29$  years and it can be concluded that the shift to older ages. Slightly dominated by females (f:m=54%:46%). The predominant localization was femur (36,72%), followed by tibia (17,5%). According to histological characteristic GCTB was classified as: grade I (29, 7%), grade II (64, 58%), and grade III (6, 25%). The main treatment was aggressive curettage, and recurrence was registered in I group (35,5%), II group (40%), III group (12,5%) and the number treated adjuvants (phenol sol.) was only 14, but without recurrence (since 2000 to 2003 year). The analysis shows a clear improvement in surgical technique and more determined approach to treatment. It turned out that it's time to recurrence is not completely predictable, but that usually occurs during the first three years, a number decreased significantly ( $X^2=10,078$ ,  $p<0,05$ ), over the years and in the last decade there were only 4 recurrences, and the occurrence of malignancies is statistically insignificant. We recorded only two cases of pulmonary metastasis, which is a proven benign nature. Rare attributes characterized by a large number of pathological fractures, and only 3 cases of multicentric. Appearance of major complication, recurrence, clearly indicates a significant increase in successful treatment, particularly using adjuvants.

**Conclusions:** And after 50 years, we can not clearly predict recurrence, we also, can not predict biological behavior of GCTB. But we can postulate benign behavior of GCTB, the occurrence of lung metastases is not a sign of malignancy GCTB. However, decreases the number of complications, in spite of the difficult conditions at times when it was very difficult to meet the demands of the modern approach in the treatment GCTB.

# HOT OR COLD? CLINICAL OUTCOME OF LIQUID NITROGEN, PHENOL, PMMA AND COMBINATIONS AS LOCAL ADJUVANT TREATMENT AFTER CURETTAGE IN GIANT CELL TUMOR OF BONE

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L van der Heijden MSc<sup>1</sup>, ICM van der Geest MD PhD<sup>2</sup>, HWB Schreuder MD PhD<sup>2</sup>, RPH Veth MD PhD<sup>2</sup>, MAJ van de Sande MD PhD<sup>1</sup>, PDS Dijkstra MD PhD<sup>1</sup>

1. Department of Orthopedic Surgery, Leiden University Medical Center, Leiden, the Netherlands
2. Department of Orthopedic Surgery, University Medical Center St. Radboud, Nijmegen, the Netherlands

**Objectives:** Curettage with local adjuvants has become standard of care in most Giant Cell Tumors of Bone (GCTB). However, main problem in the surgical management of GCTB is the high local recurrence risk after intralesional treatment. Over the last three decades, orthopedic surgeons have experimented with different combinations of phenol, liquid nitrogen and polymethylmetacrylate (PMMA) to improve oncological outcomes, but preferable local adjuvant treatment remains controversial. Aim of the present study is to determine the optimal local adjuvant treatment regarding clinical outcomes of intralesional curettage in GCTB.

**Methods:** From a total of 167 evaluated patients, 120 patients treated for GCTB between 1989 and 2009 were included in this bi-center retrospective study. Patients referred to these centers with a local recurrence, primarily treated differently or with GCTB of the axial skeleton and small bones (n=47) were excluded. Mean follow-up was 82 months (range 24-236). Patients from one center were treated with curettage, liquid nitrogen and bonegrafting (n=21) or curettage, liquid nitrogen and PMMA (n=26) and patients from the other center with curettage, phenol and PMMA (n=73). We evaluated local recurrence and complication rates in all groups. Treatment groups matched for age, gender, soft tissue extension and pathologic fractures.

## **Results:**

**Oncologic outcome:** Overall recurrence rate was 29% (35/120). Local recurrence rates for different local adjuvants were as follows: liquid nitrogen and bonegrafting 38% (8/21); phenol and PMMA 29% (21/73); and liquid nitrogen and PMMA 23% (6/26). Differences between local adjuvant groups were not significant (Log Rank; p=0.526). Mean time to local recurrence was 23 months (range 4-78).

**Surgical outcome:** Complication rates for different local adjuvants were as follows: liquid nitrogen and bonegrafting 24% (5/21), liquid nitrogen and PMMA 19% (5/26) and phenol and PMMA 10% (7/73). Complications after the use of liquid nitrogen and bonegrafting included transient nerve palsy (n=2), infection (n=1), arthrosis (n=1) and fracture (n=1); after liquid nitrogen and PMMA arthrosis (n=2), infection (n=2) and fracture (n=1) and after phenol and PMMA arthrosis (n=2), infection (n=1), chronic pain due to cement remnants (n=4) and fracture (n=1). Complication rates did not differ significantly between local adjuvant groups (Log Rank; p=0.107).

**Conclusions:** No significant differences were found between local adjuvant groups regarding local recurrence and complication rates. Treatment including PMMA resulted in lower recurrence rates, possibly indicating that PMMA is the superior of the investigated local adjuvants in this study. PMMA provides for more rigorous curettage, in part because of the necrotizing effect on the tumor cavity walls and also through its reconstructive properties. Therefore, adequate curettage should include at least PMMA as local adjuvant and cavity fill-up.

## CHONDROBLASTOMA OF THE BONE: FUNCTIONAL OUTCOME AFTER OPERATIVE TREATMENT.

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*D.P. Neophytou, J. Jagiello, M. D. Sewell, S. NgManSun, J. Skinner, R. Pollock, W. Aston, T. W. Briggs*  
*The Bone and Tumor Unit, Royal National Orthopaedic Hospital, Stanmore, UK*

**Purpose:** The purpose of this study is to review all patients with chondroblastoma that were treated in our hospital from 1980 until 2012 in an attempt to evaluate the functional outcome and to identify possible factors related to increased risk of recurrence.

**Patients and Methods:** 96 patients, 68 male and 28 female, with mean age 27.7 years (range 9-60 years) with histologically proven chondroblastoma were treated in our Hospital. We retrospectively reviewed these patients using our histopathological database, medical records, radiological imaging, and patients were followed up using conventional functional outcome measures.

The mean follow up was 7.25 years (range 2- 18 years). The presenting symptom was pain and the treatment in the majority of the patients included intralesional curettage and grafting (autograft or allograft) or the use of polymethylmethacrylate.

Functional outcome was measured with MSTS score system and their general health condition was demonstrated by the SF-12 questionnaire.

There was a wide distribution of the lesions across the skeleton but the most frequently involved sites were the epiphyses or apophyses of the long bones, especially proximal tibia, proximal humerus and distal femur.

**Results:** The mean MSTS score was 26.4 (13-30) and the mean SF-12 score was 31.37 (25-37). 11 patients (11.3%) had a histological confirmed local recurrence that was treated with further procedures and one of these patients had an elbow replacement after aggressive recurrence. No patients developed metastases.

**Conclusion:** Chondroblastoma is a rare benign bone tumor commonly presenting in adolescents and young adults that can be successfully treated with intralesional curettage and reconstruction with grafting. This study illustrates that we can achieve excellent functional outcomes, ensuring a high chance of joint preservation and a low rate of recurrence.

E. Palmerini M.D.<sup>1</sup>, E. L. Staals M.D.<sup>2</sup>, M. Alberghini M.D.<sup>3</sup>, R. G. Maki M.D. Ph.D.<sup>4</sup>, Cristina Antonescu MD<sup>5</sup>, L. Zanella M.D.<sup>3</sup>, C. Ferrari MSc<sup>4</sup>, P. Ruggieri<sup>2</sup>, P. Picci M.D.<sup>4</sup>, S. Ferrari M.D.<sup>1</sup>

<sup>1</sup>Chemotherapy, <sup>2</sup>Orthopaedic Surgery, <sup>3</sup>Surgical Pathology, Laboratory<sup>4</sup>, Musculoskeletal Oncology Department, Istituto Ortopedico Rizzoli, Bologna, Italy; Departments of <sup>4</sup>Medicine and <sup>5</sup>Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

**BACKGROUND:** Angiosarcoma is a high-grade malignant vascular tumor that can occur in soft tissue and bone (2002 WHO classification). Data on bone angiosarcoma are extremely scarce. The main treatment for primary disease is surgical intervention. The role of chemotherapy is undefined. Survival rates of malignant vascular tumors of bone are unknown.

**PATIENTS AND METHODS:** Patients with a diagnosis of bone angiosarcoma in the Bone Tumors Database of Rizzoli Institute (1980-2009) and in the Pathology Department database of MSKCC (1996-2009) were identified and clinical charts were reviewed.

**RESULTS:** Data of 60 patients were analyzed: median age 54 years (range 18-82); 38 males: 22 females; site of primary lesion: femur (37%), pelvis (23%), tibia (12%), humerus (10%); sacrum (7%), other (11%); size of primary lesion > 10 cm: 57%; 36 (60%) patients with localized disease and 24 (40%) with metastatic disease at presentation. 72% of patients underwent surgery, with 50% of patients achieving surgical complete remission (SCR). Radiotherapy (RT) was administered to 29% of patients, and chemotherapy (CT) to 67% of metastatic patients and 37% of localized patients.

With a median follow-up of 10 years (range 1-25), the 5-year overall survival rate (OS) was 20%(95%CI 9-30%); 33%(95%CI 17-50%) for patients with localized disease and 0 for patients with metastatic disease,  $P<0.0001$ ; 40%(95%CI 22-58%) in patients with SCR, and 0 for those with no SCR,  $P<0.0001$ . 5-year OS in localized patients: males 40%(95%CI 20-61%), females 20%(95%CI 0-44%),  $P<0.3$ ; age < 26: 50%(95%CI 0-100), age 26-65: 36%(95%CI 17-56%), age >65: 17%(95%CI 0-46%),  $P=0.5$ ; adjuvant CT: 49% (95%CI 20-78), no adjuvant CT: 39% (95%CI 15-63),  $P=0.15$ . RT was only adopted in 5 patients with localized disease (4 of them with inadequate margins); none of them was alive at 5 years. Patients with metastatic disease received different CT regimens, most of them based on doxorubicin/cisplatin (73%) and paclitaxel (27%). In 13 of the 16 patients evaluable for response 2 PR were documented: 1 with PEGylated liposomal doxorubicin, and 1 with paclitaxel.

**CONCLUSIONS:** Metastatic bone angiosarcoma is invariably fatal. SCR is key factor for survival. It is possible that gender influences prognosis as well. A trend towards a survival advantage for the use of adjuvant CT was shown.



## CLINICAL OUTCOME OF MYXOFIBROSARCOMA

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Robert Nakayama<sup>1</sup> robert@a2.keio.jp, Kazutaka Kikuta<sup>2</sup>, Michiro Susa<sup>1</sup>, Itsuo Watanabe<sup>1</sup>, Keisuke Horiuchi<sup>1</sup>, Yoshihisa Suzuki<sup>2</sup>, Ukei Anazawa<sup>3</sup>, Hiroo Yabe<sup>1</sup>, Yoshiaki Toyama<sup>1</sup>, Hideo Morioka<sup>1</sup>

1) Department of Orthopaedic Surgery, School of Medicine, Keio University, Tokyo, Japan

2) Department of Orthopaedics, Kyosai Tachikawa Hospital, Tokyo, Japan

3) Department of Orthopaedic Surgery, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan

**Objectives:** Myxofibrosarcoma (MFS), previously called myxoid malignant fibrous histiocytoma, is a soft tissue sarcoma that typically affects the extremities and the trunk of the elderly. The number of patients diagnosed with MFS has been increasing in Japan's aging society, and now it is one of the most common tumors among the diverse soft tissue sarcomas. In order to find the prognostic factors that may affect the clinical outcome, we retrospectively analyzed the clinical data of patients with MFS with emphasis on the location of the tumor at presentation.

**Materials and Methods:** Since 1999, there were 38 cases of MFS, including recurrent tumors, in our database. Investigative factors included age, gender, location of the tumor at presentation (deep or subcutaneous, extremities or trunk), and surgical margin.

**Results:** There were 24 males and 14 females, and the age at diagnosis ranged from 38 to 88 years old (avg. 64.4). The follow-up period ranged from 5 to 210 months (avg. 62.1). Nine patients (23.7%) had the tumor in the trunk, whereas 29 patients (76.3%) did in the extremities, (6 (15.8%) in the upper limb and 23 (60.5%) in the lower limb). 25 cases (65.8%) arose in the subcutaneous fat layer with or without fascial involvement and they were more likely to undergo unplanned surgery before referral to our service than those which arose beneath the fascia ( $P=0.0021$ ). 13 patients (34%) developed local recurrence, and the interval between initial surgery and the first local recurrence ranged from 10 to 147 months (avg. 38.7). The 5-year tumor free survival was only 54%, and seven patients (18.4%) underwent amputation during their clinical course. Oncological outcomes were 24 CDF, 6 NED, 4 AWD, 3 DOD, and 1 DOOD. Although seven patients (18.4%) developed distant metastases, only one case died of disease due to the metastatic lesion, whereas the remaining three died due to failure in local control.

**Conclusions:** MFS is infamous for its extreme invasiveness and this study highlighted the difficulty in management of local control. For improvement of the clinical outcome, novel methods need to be established to evaluate the infiltrated area in both histological and radiological ways to determine the adequate surgical margin. Furthermore, novel multidisciplinary treatment is needed to reduce the recurrence as well as to treat the recurrent tumors.

# ATYPICAL HISTOPATHOLOGY OF BENIGN NOTOCHORDAL CELL TUMOR: FURTHER EVIDENCE FOR A LINK TO CHORDOMA?

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Frederique Larousserie, Jennifer Kreshak, Marco Alberghini, Stefano Boriani, Joseph Mirra, Daniel Vanel

All authors are affiliated with the Istituto Ortopedico Rizzoli, Bologna, Italy

**Objectives:** Notochordal remnants have been documented in the intervertebral disk and as small soft tissue masses found extraosseously in the craniosacral spine. More recently, notochordal-like lesions in the vertebrae have been better characterized and controversy exists as to whether they may be precursors to chordoma. Various terms have been used, including giant notochordal rest and benign notochordal cell tumor (BNCT). They have been described as having morphological features distinct from fetal notochordal cells, notochordal cells found in disks, and chordomas. This study was conducted to identify BNCTs that might have previously been diagnosed as chordoma and to better delineate any possible relationship between these two entities.

**Materials and Methods:** All cases of chordoma without significant soft tissue masses diagnosed at our institution prior to the recognition of BNCT were re-reviewed. Three of these chordomas included areas of BNCT. All three cases underwent vertebrectomy for the diagnosis of chordoma, ensuring adequate sample size for evaluation.

**Results:** Two lesions were found to have distinct areas of both chordoma and BNCT, as well as atypical areas that do not definitively meet the criteria for BNCT or chordoma. The third case did not have any clear areas of chordoma but consisted of what would now be called BNCT according to published criteria, however, a small atypical area was seen inside the lesion. This case ultimately recurred as a chordoma. All cases were positive for brachyury in all areas of the lesion.

**Conclusions:** While BNCT is now a well-recognized entity, its origin and relationship to chordoma continues to be controversial. BNCT appears to have all the characteristics of a benign lesion, is more prevalent than chordoma, and has been documented in several cases to be stable over long periods of time, however, chordomas have been found immediately adjacent to some BNCTs. These three cases indicate progressive change from benign to malignant within the same lesion, providing further evidence for a link between the two and the possibility for transformation of BNCT. Under the best of circumstances, histopathologic discrimination between these entities can be challenging; these cases highlight the need for adequate, accurate biopsy and close clinical follow-up.

# MULTIPLE HEREDITARY EXOSTOSES: FIRST STUDY IN A COHORT OF LATIN AMERICAN PATIENTS

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Segura, F. 1, Delgado, M.A.2, Sarrión, P.3, Azar, N.2, Zecchini L.4, Bistué Millón, M.B.2  
Chiesa, M.5; Robledo, H.5; Dodelson de Kremer, R. 2; Ballcels, S 3; Grinberg, D.3; Asteggiano, CG. 2,6,7.

(1) Cátedra de Ortopedia y Traumatología. Universidad Nacional de Córdoba. Argentina

(2) CEMECCO (Centro de Estudio de las Metabolopatías Congénitas), Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Hospital de Niños S.T., Córdoba, Argentina; (3) Departamento de Genética, Facultad de Biología, Universidad de Barcelona, España; (4) Servicio de Traumatología, Hospital de Niños S.T., Córdoba, Argentina; (5) Servicio de Bioimágenes, Hospital de Niños S.T., Córdoba, Argentina. (6) Cátedra Química Biológica, Facultad de Medicina, Universidad Católica de Córdoba, Argentina; (7) Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

Multiple Hereditary Exostoses (MHE) is an autosomal dominant disorder characterized by the formation of cartilaginous bone tumors (osteochondromas) at multiple sites. The most severe complication is malignant transformation to chondrosarcoma. Defects result from mutations in EXT1(8q24) or EXT2(11p11.2) genes, which encode glycosyltransferases necessary for the synthesis of heparin sulfate proteoglycans (HSPGs). This study represents the first investigation of the genotype-phenotype correlation in Latin American patients. We have studied 25 MHE patients with ages ranging from 2 to 50 years old. PCR and direct sequencing of both genes were performed after the written consents. Clinical assessments and functional rating were analyzed (Musculoskeletal Tumor Society Scale).

A total of 10 exonic changes were identified. Six were novel mutations in EXT1 (p.Leu251Stop/p.Leu283Stop/p.Arg346Thr/p.Lys126AsnfsX62/p.Lys306Stop/p.Leu264Pro) and two in EXT2 (p.Trp393Stop/p.Asp307ValVfsX45). Two mutation were previously described in EXT1 (p.Leu490ArgfsX9 and p.Val78ArgfsX111) (<http://medgen.ua.ac.be/LOVD/home.ph>). Missense novel mutations were analyzed by prediction programs. Clinical study: 8 patients presented a severe phenotype ranging from IS to IVS and 2 a mild one. A novel mutation p.Leu283Stop was associated with a malignant transformation to chondrosarcoma. We could not find a correlation between EXT1 and EXT2 genes with the grade of severity. Our results identified novel mutations in a first cohort of Latin American patients. Preliminary analysis indicated that mutations on the first EXT1 exons correlate with a more severe phenotype. This interdisciplinary study represents the first genotype-phenotype investigation in Argentina and its progression will provide a wider vision of this pathology in our country and Latin America. CONICET/FONCYT-PICT2350/UCC.

EXT1:

p.Leu251Stop;

p.Leu283Stop;

p.Arg346Thr;

p.Lys126AsnfsX62;

p.Lys306Stop;

p.Leu264Pro;

p.Leu490ArgfsX9;

p.Val78ArgfsX111

EXT2:

p.Trp393X;

p.Asp307ValVfsX45

# CAN CONTRAST-ENHANCED ULTRA SONOGRAPHY (CEUS) DISTINGUISH BENIGN FROM MALIGNANT SOFT-TISSUE MASSES? PRELIMINARY RESULTS

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Armanda De Marchi, Simona Pozza, \*Elena Brach del Prever, \*\*Alessandra Linari, , Paola De Petro, Federica Gunetti, \*\*\*Raimondo Piana, \*\*\*Gian Carlo Gino, Carlo Faletti.

Department of Radiology, AO CTO/Maria Adelaide of Turin, Italy

\*Department of Traumatology, Orthopaedics and Health Medicine, University of Turin, Italy

\*\*Department of Pathology, AO OIRM-S. Anna of Turin, Italy

\*\*\*Department of Oncological Orthopaedics and Reconstructive Surgery, AO CTO/Maria Adelaide of Turin, Italy

**Background:** Malignant masses are characterized by anarchic vascularisation related with neoangiogenesis. The evaluation of presence/absence of vascularisation could be an easy and early method to identify masses potentially malignant. Power Doppler study identify only major vessels, but is unable to visualize the diffuse vascular pathological network. We hypothesized that vascular enhancement identified by contrast-enhanced ultra sonography (CEUS) could be useful to discriminate between benign and malignant lesions.

**Materials and methods:** A retrospective cohort series of 207 patients from January 2009 to December 2010 with soft tissue masses of limbs and trunk were studied by US, PD and CEUS: the intravenous contrast agent was SonoVue® (Bracco, Milan, Italy). All patients gave their informed consent. Each lesion was scored on the following characteristic: presence or absence of vascularisation, homogenous or inhomogenous enhancement with avascular areas, peripheric enhancement, spare intralesion vessels and lesion's vascular time. In all cases the histological diagnosis was done on surgical definitive specimens or on biopsy. The CEUS vascular patterns were compared with the histological results.

**Results:** 88 benign and 117 malignant lesions were diagnosed by histology. In all masses, seven different CEUS patterns were observed and three different vascular timing. 90% of the malignant lesions (105/117) show a rapid early time of vascularisation (arterial phase) and 60% (70/117) an inhomogenous enhancement pattern with avascular areas. Only 20% of benign lesions (11/88) shows a pattern similar to malignant lesions and 50% (44/88) showed a rapid time vascularisation: histologically, these last arterial pattern was characteristic of arterio-venous malformation and hemangioma.

**Conclusions:** The inhomogenous CEUS enhancement pattern with avascular areas and the rapid vascular flow can be related with malignancy; other CEUS pattern are more frequent in benign lesions; rapid arterial flow in benign masses are present when hemangioma or artero-venous malformation are present. These preliminary results suggest that CEUS can facilitate a rapid and easy identification of masses potentially malignant, therefore CEUS could be considered as a first level exam, before more complex and expensive imaging. If core needle biopsy is indicated, CEUS study could increase the sensitivity and sensibility (De Marchi et Al. Eur Rad 2010). Further investigations with a larger cohort of patients is mandatory.

# PROGNOSTIC RELEVANCE OF 18F-FDG UPTAKE IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMA OF THE EXTREMITIES UNDERGOING NEOADJUVANT TREATMENT

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D. Andreou<sup>1</sup>, H. Boldt<sup>2</sup>, B. Jobke<sup>3</sup>, M. Werner<sup>4</sup>, D. Pink<sup>5</sup>, M. Niethard<sup>1</sup>, F. Traub<sup>1</sup>, P. Reichardt<sup>5</sup>, P.U. Tunn<sup>1</sup>

<sup>1</sup> Department of Orthopedic Oncology, Helios Klinikum Berlin-Buch, Sarcoma Center Berlin-Brandenburg, Berlin, Germany; <sup>2</sup> Department of Nuclear Medicine, Helios Klinikum Berlin-Buch, Berlin, Germany; <sup>3</sup> Department of Radiology, Helios Klinikum Berlin-Buch, Berlin, Germany; <sup>4</sup> Department of Pathology, Helios Klinikum Emil von Behring, Sarcoma Center Berlin-Brandenburg, Berlin, Germany; <sup>5</sup> Department of Hematology, Oncology and Palliative Care, Helios Klinikum Bad Saarow, Sarcoma Center Berlin-Brandenburg, Bad Saarow, Germany

**Objectives:** The management of locally advanced soft tissue sarcomas of the extremities can be challenging and neoadjuvant treatments are often needed to improve local control and disease outcome. The objective of this study was to evaluate in a prospective setting whether 18F-FDG-PET can accurately predict prognosis in patients with locally advanced soft tissue sarcoma of the extremities undergoing neoadjuvant isolated limb perfusion (ILP) with TNFa and melphalan.

**Materials and methods:** 33 consecutive patients with locally advanced non-metastatic high-grade soft tissue sarcoma of the lower (n=26) and upper (n=7) extremity underwent 18F-FDG-PET or PET/CT prior to and 6 weeks after neoadjuvant ILP between 2006 and 2009. 24 patients presented with a primary tumor and 9 patients with a local recurrence. Mean follow-up amounted to 28 months. Non-parametric analyses were performed with the Mann-Whitney U test. Survival curves were calculated with the Kaplan-Meier method and compared with the log-rank test.

**Results:** The mean and median maximum standardized uptake value (SUVmax) amounted to 9.3 and 6.3 prior to treatment (SUVmax1), compared to 5.7 and 3.1 after 6 weeks (SUVmax2), respectively. 9 patients developed regional or distant metastases after a mean of 8.8 months, 3 of whom died of their disease. Patients who did not develop metastases had a mean SUVmax1 of 8.6 (range, 1.5 – 27.1) and a mean SUVmax2 of 5.4 (range, 1.0 – 30.6). Patients who developed metastatic disease had a mean SUVmax1 of 11.2 (range, 3.6 – 35.5) and a mean SUVmax2 of 6.6 (range, 2.0 – 12.2). These differences were not statistically significant ( $p = 0.505$  for SUVmax1 and  $p = 0.109$  for SUVmax2). Patients with a SUVmax1  $> 6.3$  had a metastasis-free survival of 67.4% after 2 years, compared to 72.2% for patients with a SUVmax1 of  $\leq 6.3$  ( $p = 0.530$ ). However, patients with a SUVmax2 of  $> 3.1$  had a metastasis-free survival of 50.8% after 2 years, compared to 86.7% for patients with a SUVmax2 of  $\leq 3.1$  ( $p = 0.05$ ).

**Conclusions:** SUVmax prior to treatment does not appear to correlate with prognosis in patients with locally advanced non-metastatic high-grade soft tissue sarcomas of the extremities. However, a low SUVmax 6 weeks following ILP was associated with an improved metastasis-free survival in this study. These results need to be validated in larger studies with longer follow-up, before definitive conclusions on the role of 18F-FDG-PET in this setting can be drawn.

# IS [F-18]-FLUORODEOXY-D-GLUCOSE POSITRON EMISSION TOMOGRAPHY (PET) OF VALUE IN THE MANAGEMENT OF PATIENTS WITH CRANIOFACIAL BONE SARCOMAS UNDERGOING NEOADJUVANT TREATMENT? A SINGLE INSTITUTION EXPERIENCE.

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Anna Maria Frezza, Tim Beale, Jamshed Bomanji, Amrita Jay, Simon Morley, Nicholas Kalavrezos, Palma Dileo, Jeremy Whelan, Sandra Strauss

The London Sarcoma Service, University College of London Hospital - London, England

**Objectives:** We evaluated the role of PET/CT used to assess response to preoperative chemotherapy in patients with primary craniofacial bone sarcomas.

**Patients and methods:** Thirteen patients with craniofacial sarcomas (12 patients with osteosarcoma) presenting between 2005 and 2011 were retrospectively evaluated. All patients received up to 6 cycles of standard preoperative chemotherapy followed by the resection of the primary tumour. Response to treatment was assessed using MRI (evaluated according to RECIST criteria) and PET/CT (evaluated according to EORTC guidelines), performed at least at baseline, after 2 to 3 cycles of treatment and pre-operatively.

**Results:** The median baseline PET SUV value was 10 (range 0-41); in 2 patients no uptake was detected. The preoperative PET, compared with the baseline, proved a PMR in 6 patients (55%), a CMR in 2 (18%) and SMD in 3 (27%). Conversely, only one patient achieved a RECIST response on MRI: 12 (92%) had SD. One patient underwent early resection due to clinical progression after an initial response to treatment. This was confirmed by PET (SUV from 21 to 42) but not on MRI. Eleven of 13 patients (85%) had <90% histological necrosis the in resected tumour. With a median follow-up 23 months, 10 patients (77%) remain disease free, two had metastatic progression (15%) and 1 relapsed locally (8%). The overall median DFS was 17 months. For those patients who achieved a response to preoperative PET the median DFS was 18 months compared with 3 months in those who did not ( $p=0.003$ ). Conversely, the median DFS did not differ according to histological response (19 versus 17 months, >90% versus <90% necrosis). Resection margins were also found not to correlate with survival (18.5 months for R0 versus 17.5 months for R1,  $p=0.20$ ).

**Conclusion:** PET/CT appears more reliable than standard imaging in evaluating response to neoadjuvant chemotherapy in craniofacial bone sarcomas, changed management in one patient, and in this small retrospective series, correlated better with patient outcome than histological response and resection margins.



## CT VERSUS PET IN THE DIAGNOSIS OF GANGLIONAR METASTASIS OF SOFT TISSUE SARCOMAS

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*Casanova, José; Fonseca, Ruben; Simões, Pedro; Lapa, Paula; Ruivo, Catarina; Tavares, Paulo; Laranjo, António and Freitas, João.*

*Coimbra University Hospital – Coimbra - Portugal*

**Objectives:** Ganglionic metastases in soft tissue sarcomas are not common, but when present are associated to a worse prognosis. CT was used for the detection of ganglionic involvement in soft tissue sarcomas, but since 2005 PET-CT was included as a diagnostic tool for this specific diagnosis. The objective of the present study is to compare both imaging techniques in a group of patients also submitted to surgery of ganglionic resection based on the presumptive diagnosis obtained with the referred imaging studies.

**Material and methods:** between 2005 and 2011, 52 soft tissue sarcoma patients were diagnosed also with metastatic ganglionic involvement, and submitted to surgery that included ganglionic resection, and their surgical specimens were studied for specific detection of ganglionic metastasis. 31 patients were female, 21 were male, with a median age of 53,6y. Locations of the primary lesions were axial in 24 patients and extremities in 28. The most frequent diagnosis was liposarcoma, synovial cell sarcoma and soft tissue Ewing sarcoma. 40 patients (76,9%) were submitted in the same week to both exams, and 12 patients have the exams done with an interval superior to 3 weeks, and their results were excluded because of the time frame difference. A statistical analysis was performed using SPSS-19 version, and a Fisher exact test was used to compare results.

**Results:** The Fisher exact test was statistically significant when comparing the results of both imaging techniques ( $p < 0,010$ ), not statistically significant ( $p < 0,472$ ) when comparing the detected presence of ganglionic involvement in CT with the respective positivity in the surgical specimens, and statistically significant ( $p < 0,006$ ) when comparing PET-CT results with the positivity in the surgical specimens. CT specificity was of 40% and sensitivity of 75% and a positive predictive value of 75% and a negative predictive value of 40%. PET-CT specificity was of 83,3% with a sensitivity of 86,7%, and a positive predictive value of 92,8% and a negative predictive value of 71,4%.

**Conclusions:** PET-CT has a significant positive predictive value, and higher specificity and sensibility in detection of ganglionic metastasis in soft tissue sarcomas.

Wanke-Jellinek E<sup>1</sup>, Domayer S<sup>1</sup>, Apprich S<sup>2</sup>, Nöbauer I<sup>2</sup>, Dominkus M<sup>1</sup>, Windhager R<sup>1</sup>, Funovics P<sup>1</sup>, Trattnig S<sup>2</sup>

1 Medical University of Vienna - Department of Orthopaedic Surgery - Vienna General Hospital - Austria

2 Medical University of Vienna - Department of Radiology - Vienna General Hospital - Austria

**Objectives:** As the histological entity of a chondroid lesion strongly influences the type of surgical intervention, pre-operative diagnostic procedures aim to clearly distinguish between chondroma, low-grade chondrosarcoma and high-grade chondrosarcoma before therapy is initiated. However, benign and malignant chondrogenic tumours concur in some clinical and imaging features. In recent literature the need for more precise tools for the comprehensive evaluation of chondrosarcomas was postulated. The aim of this feasibility study was to evaluate the application of quantitative MR mapping technology at 3T in the assessment of chondrogenic tumours. We hypothesized that T1 values of chondroma show a similar behavior to those of normal cartilage, implicating that the uptake of contrast agent is quantitatively depictable. Furthermore we presumed that chondrosarcoma showed a different pattern concerning the kinematics of the contrast medium.

**Materials and Methods:** 6 consecutive patients (1 male; 5 female; mean age 53 years, range 33 - 71 years) with chondroid tumors around the knee were selected to enter the study. All MRI examinations were performed on a 3.0 Tesla whole body Magnetom TimTrio scanner (Siemens Healthcare, Erlangen, Germany). Patients first obtained a non-contrast baseline measurement including the morphologic sequences and the T1 mapping sequence. The contrast agent was given intravenously in double dose (0.2mmol/kg body weight; Magnevist, Berlex-Schering, Berlin, Germany), and the T1 mapping protocol was repeating under maintenance of the positioning and field-of-view planning at 30, 60 and 90 minutes. A region of interest (ROI) was manually defined on native T1 map images. Analysis was performed on 3 consecutive slices in which the lesion was depicted at its largest diameter and consisted of a global area (surrounding the whole lesion), a central area (representing the central part of the lesion) and a circumferential area (global minus central area). Subsequently, the mean signal intensity (in ms) of the ROI was measured and evaluated over time for each patient. Central and peripheral T1 values were compared for all time points (before contrast, 30, 60 and 90 minutes).

**Results:** Histological evaluation of the retrieved specimens revealed 4 chondromas and 2 chondrosarcomas (grade 2). The mean T1 value for chondromas was 1596ms in the central, and 1728ms in the circumferential areas before application of contrast agent. At 30, 60 and 90 minutes after application the central values were 591ms, 628ms and 672ms, and 620ms, 651ms and 719ms in circumferential areas. There was no significant difference between the central and circumferential areas ( $p < 0.001$ ).

Before the application of contrast agent mean T1 values in chondrosarcomas were 2435ms centrally and 2001ms circumferentially. After 30, 60 and 90 minutes the values were 2623ms, 2069ms and 1550ms in the central parts, and 840ms, 735ms and 734ms in the circumferential parts. Consequently there was a difference in contrast agent uptake between chondromas and chondrosarcomas.

**Conclusion:** Albeit we cannot draw conclusions to contrast agent kinematics in chondroid tumours in general, an additional diagnostic modality arises out of the application from validated and well-established T1 algorithms to evaluate dignity of chondroid lesions. Further studies and larger case series will be needed in order to optimize MR-algorithm and evaluate clinical applicability.

## THE ROLE OF MRI IN ASSESSMENT OF PATIENTS WITH SOFT TISSUE LESIONS IN SARCOMA CENTER

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*Olga Zaikova, Ingeborg Taksdal, Sigmund Skjeldal, Ole-Jacob Norum, Simen Sellevold, Joackim Torkildsen, Kirsten Sundby-Hall*  
*Norwegian Radium Hospital, Oslo University Hospital, Norway*

**Objectives:** Patients with soft tissue sarcomas (STS) should be referred to sarcoma centers without previous biopsy or surgery. However, most patients with soft tissue lesions (lumps and clumps) have benign diagnosis. The challenge in organizing a sarcoma service is to identify STS patients without delay and to minimize resources used on patients who do not need treatment at the sarcoma center. MRI is becoming a widely used diagnostic tool in patients with soft tissue lesions. The aim of the present study was to evaluate the role of MRI when selecting patients with soft tissue lesions for investigation and treatment in sarcoma center.

**Materials and Methods:** During 2010, 746 patients older than 15y.o. with soft tissue lesions in extremities and trunk wall were referred to our center. 634 (85%) of the referrals had MRI enclosed. All MRI were re-evaluated by dedicated sarcoma radiologists, described and then discussed in a multidisciplinary team. The preliminary radiological diagnosis were divided into following categories: (1) subcutaneous lipoma; (2) deep lipoma or low-grade liposarcoma; (3) not neoplastic or benign lesion without need of biopsy; (4) most probably benign lesion, but biopsy need for confirmation; (5) sarcoma; (6) other malignancy. The multidisciplinary team worked out a plan for further diagnostics and treatment for each patient. For the purpose of this study the patients' medical records were retrospectively reviewed and preliminary diagnoses suggested by radiologists at referral were compared with the final diagnoses. Follow-up time was one year or longer for all patients.

**Results:** The suggested radiological diagnoses were: (1) subcutaneous lipoma in 144 (23%) patients, surgery at local hospital was recommended, non of these patients had malignant diagnosis after one-year follow-up; (2) deep lipoma or low-grade liposarcoma in 149 (24%) patients, surgery without biopsy was recommended, 8 patients in this group had histopathological diagnoses low grade liposarcoma; (3) not neoplastic or benign lesion without need of biopsy in 70 (11%) patients, non of these patients have got diagnosis converted to malignant; (4) most probably benign lesion, but biopsy need for confirmation in 185 (29%) patients, 7 of these patients had sarcoma, 4 patients had other malignancy, 161 had benign lesion and in 13 the biopsy was not performed; (5) sarcoma in 72 (11%) patients, of these patients 33 had STS while 11 and 28 patients had other malignancy and benign lesion respectively ; (6) other malignancy in 14 (2%) patients, in 12 of these patients other malignancy was confirmed by histopathology. Consequently, based on MRI the biopsy could be omitted in 363 of 746 (48%) referred patients.

**Conclusions:** MRI alone cannot separate between benign and malignant lesions (except lipomas and a subgroup of other soft tissue lesions of non-neoplastic appearance). However, MRI is a safe method for selecting of patients who do not need to attend the sarcoma center in person and in priority of resources at sarcoma center.

Boffano Michele<sup>1</sup>, Albertini Ugo<sup>1</sup>, Marone Stefano<sup>1</sup>, Boux Elena<sup>1</sup>, Robba Tiziana<sup>2</sup>, Faletti Carlo<sup>2</sup>, Gino Gian Carlo<sup>1</sup>, Brach del Prever Elena<sup>1</sup>, Piana Raimondo<sup>1</sup>

<sup>1</sup> Oncologic and Reconstructive Orthopaedics – AO CTO/Maria Adelaide Torino, Italy

<sup>2</sup> Imaging Department – AO CTO/Maria Adelaide Torino, Italy

**Objectives:** Lipomatous tumours are the commonest soft tissue lesions. The aim of the study is to evaluate whether a correct Imaging study can drive to a 'histologic diagnosis' and when a biopsy is still needed.

**Materials and Methods:** We retrospectively reviewed all the lipomatous tumours treated in the Oncological and Reconstructive Orthopaedics Department of the AO CTO/M. Adelaide in Torino (Italy) from January 2003 to December 2009. Imaging studies (either MR or CT) underwent an accurate analysis from a blinded radiologist with expertise in musculoskeletal oncology and afterwards compared with final histologic reports. The accuracy of the sequences obtained, the contrast medium enhancement, the dimensions of the lesion, the percentage of fat tissue, the characteristics of septa and margins were considered as parameters. Exclusion criteria were: subcutaneous lipoma, lipoma of small dimensions (greater dimension < 10cm), incomplete Imaging study.

**Results:** Sixty-six individuals were included in the study. The histologic diagnosis based on Imaging and compared with the pathologic report was correct in 73%. In 4 cases it was not possible to identify a subtype of liposarcoma, 2 cases were downstaged from pleomorphic to myxoid, 3 cases were upstaged from pleomorphic to myxoid and from myxoid to atypical lipomatous tumour (ALT). The commonest mistake was to mismatch lipoma and ALT (in 8 cases out of 9 the lesion was erroneously considered an ALT instead of a lipoma).

**Conclusions:** The surgical treatment of ALT and lipomas (deep to the fascia, at least 1 dimension > 10cm) is the 'shelling-out' of the lesion in both cases. Excluding the cases of mismatch between ALT and lipoma, the mistakes were only 13.6%. We suggest that the biopsy should always be performed in low grade and higher grades lesions because they can benefit from adjuvant therapies. In this point of view no mistake could have affected the treatment and the prognosis. Imaging studies can drive to a 'histologic diagnosis' in a high number of cases, further studies are necessary to define specific patterns of lesion.

# INTRALESIONAL RESECTION MARGINS IN BONE SARCOMAS: WHY AND WHAT IS THE OUTCOME?

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Amit Kotecha, Paul Fenton, L Jeys, A Abudu, S Carter, R Tillman, R Grimer

Royal Orthopaedic Hospital, Birmingham, UK

**Objectives:** Surgical resection margins are important for the prognosis and outcome in bone sarcomas. The aim of the study was to find out the rate, causative factors and outcomes of intralesional margins on bone tumour from a large series of primary bone tumour.

**Methods:** We identified 3514 bone sarcoma patients were reviewed in our unit from 1970 and 2011. There were 2780 that were newly diagnosed bone sarcomas. The inclusion criteria for this study were; a) Detailed knowledge of size of surgical and pathological margins. b) Details of surgical procedures performed available, leaving 1955 patients in the study group. Demographic details, prognostic factors and outcomes were analysed.

**Results:** Mean age at diagnosis was 29 years (range 1 year to 100 years), with the most common diagnosis was osteosarcoma (n=1057), Chondrosarcoma (n=355) and Ewing's sarcoma (n=263). The most common sites were femur (n=882), tibia (n=388), humerus (n=226) and Pelvis (n=222). The mean size of the sarcoma was 10.6 cm.

The rate of intralesional margins significantly varied by diagnosis with Adamantinoma 31%, chondrosarcoma 28%, chondrosarcoma 25%, chordoma 19%, de differential ewings 9%, osteosarcoma 8%, other 15%. It was significantly lower in tumour where chemotherapy was used and out of all Intralesional margin of resection 70 % of cases were observed in cases with poor tumour necrosis (less than 90% tumor necrosis, p= 0.04). The rate also varied by operation type with Amputation 7%, EPR 16%, Excision alone 25%.

There were 343 cases of local recurrence. The frequency of local recurrence as increased with narrower margins (Intralesional 35%, Marginal 21%, Wide 12%, wide contaminated 32%, p=0.0001). Of those patients who had intralesional margins further surgery was undertaken with Amputation 15%, Curettage 0.4%, EPR 11%, Excision 16%, None 58%. The 5 year survival following wide contaminated margin 32%, intralesional resection was 49%, marginal 54%, and wide 70%.

**Conclusions:** Intralesional margins represent a poor independent prognostic factor for survival and local recurrence. Some tumour types and poor response to chemotherapy also contribute to the rate of intralesional margins.

Rob Grimer and Lee Jeys

**Aim:** Staging of any patient with a newly diagnosed cancer is essential. Both the Enneking staging system and the TNM are in common use. We wished to identify which was more helpful in identifying prognosis.

**Method:** Patients with data stored in a prospective database were grouped according to both the Enneking and the TNM systems and their outcomes in terms of survival were compared.

**Results:** 3838 patients had both Enneking and TNM stages of whom 1583 had a bone sarcoma and 2255 a STS. For both bone and STS the presence of metastases at diagnosis was the worst prognostic factor (HR >3). For bone sarcomas the most important prognostic factors were increasing age (HR 1.013), high grade (HR 2.56), size >8cm (HR 1.86), extra compartment spread (2.86) (all  $p < 0.0001$ ) and sex (female HR 0.87). On multivariate analysis (excluding those with metastases at diagnosis) size, age and grade remained highly significant ( $p < 0.001$ ) whilst extracompartmental spread was slightly less so ( $p = 0.0085$ ). For STS the most important prognostic factors were increasing age (HR 1.016), high grade (HR 5.0), size >5cm (HR 2.11), extra compartment spread (1.69), depth (HR = 2) (all  $p < 0.0001$ ) and extracompartmental spread ( $p = 0.0085$ ). On multivariate analysis (excluding those with metastases at diagnosis) size, age, depth and grade remained highly significant ( $p < 0.001$ ) whilst extracompartmental spread was slightly less so ( $p = 0.001$ ).

**Conclusion:** TNM staging proved slightly better and provided a wider range of survival with clear differences between the groups. It should supersede the Enneking stage.



## THE NURSE ROLE AND COMPETENCIES IN ONCOLOGY CLINICAL RESEARCH

*E. Marchesi (Istituto Ortopedico Rizzoli, Bologna, Italy)*

Clinical trials are essential for the identification of new therapy especially in oncology. Scientific rigourousness and integrity are the basis for the compliance of clinical trial regulation and data validation. The effective conduct of oncology trials requires involvement of a variety of personnel. Clinical research nurses are a key collaboration in the implementa of clinical research and play an important and strategic role acting as link between patient and the clinical staff.

In this scenario, different skills and competencies are needed to fulfill this requirement.

Clinical trial nurse compentencies in oncology include fundamental knowledge and expertise to manage patient participation in a clinical trial, to ensure patient data protection and scientific integrity and reliability to regulatory mandates, as well as protocol and ethical compliance, clinical related communication, site coordination and data collecting skills.

Although the specific job profile of a Clinical Research Nurse is not implemented in all countries, all nurses dealing with oncology trials should make an effort to deveolop specific competencies in Clinical Trial management in order to provide a better and more focused service to patients and clinical research.

*Julie Woodford, Macmillan Nurse Consultant, Royal National Orthopaedic Hospital, Stanmore. Lin Russell, Nurse Consultant Royal Orthopaedic Hospital, Birmingham*  
*Royal Orthopaedic Hospital, Birmingham and the Royal National Orthopaedic Hospital, Stanmore*  
*Contact: Lin Russell, Nurse Consultant Royal Orthopaedic Hospital, Birmingham*

There has been increasing evidence within the UK that patients with rarer cancers and in particular, those patients with sarcoma have a worse experience throughout their cancer journey when compared to patients with more common cancers and often, information needs are not met.

This paper will present a project undertaken in collaboration by the UK National Commissioned Bone Sarcoma Centres. The project aimed to ensure that all patients (and their carers) who are diagnosed with a bone sarcoma within the UK will be offered high quality, appropriate and timely information to support face to face communication throughout their cancer journey.

The project has involved undertaking a scoping exercise to complete a baseline review of the available information resources for bone sarcoma. Patient and carer workshops have been held across the UK and one-to-one interviews have been undertaken to evaluate the current patient literature.

The result is to have a universal information resource for all UK bone sarcoma patients that is current and up-to-date, that contains appropriate information that can also be accessed electronically in addition to being provided from specialist centres. The use of the Patient Information Prescription tool will also provide a patient record of information provision and assist with peer review monitoring.

This project encompasses other continuing national initiatives to improve the patient experience from the point of a suspected cancer diagnosis, to treatment and throughout survivorship and possible relapse and advanced disease. These include embracing user involvement, implementing advanced communication skills training for professionals and undertaking holistic needs assessments for patients.

## PREPARATION AND NURSING ASSISTANCE IN THE OPERATING ROOM IN SACRAL RESECTIONS FOR BONE TUMORS.

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Macchia N, Mazza E, Rocchegiani L

Operating Room Service and Orthopedic Oncology Department, Istituto Rizzoli, Bologna, Italy.

**Introduction:** Primary tumors of the sacrum are rare; most frequent are giant cell tumor and chordoma. Surgery of giant cell tumors is intralesional excision, chordomas require resection of the sacrum. Sacral resections are complex and require careful preparation and continuous assistance from the all team, including anesthesiologic and surgical team, in the operating room. The aim of our study was to review the experience of the IV Department of Orthopedics with sacral resections, trying to analyze the crucial steps for preoperative preparation, intraoperative assistance, complications and results.

**Material and Methods:** From 1976 to 2010 71 patients underwent a sacral resection for chordoma, 42 males and 29 females, with mean age 54 years. Fortyeight resections were proximal to S3, while 23 distal to S3. Most of the proximal resections had a combined anterior and posterior approach, all the distal had only posterior approach. Details of positioning of the patients and anesthesiologic preparation were analyzed and oncologic results, surgical and anesthesiologic complications were reviewed, at a mean follow up of 9.5 years.

**Preoperative anesthesiologic preparation:** the patient preparation starts at the anaesthetic room and strictly follow the anaesthetical issues: once the anaesthetic technique is defined, the vital functions monitoring is carried out, it is a non-invasive procedure and shows: ECG, FC, NBP, SPO2, ETCO2 and the position of intravenous accesses. Most importance must be given to IBP (Invasive Blood Pressure) which gives a constant measurement of blood pressure and allows the fulfilment of the Blood Gas Analysis. A central venous catheter and a urinary catheter are inserted, the body temperature is monitored through a esophageal temperature probe, it prevents risks of hypothermia. In the end it is important to recommend the use of the CARDIOQ or VIGILEO monitoring for the visualization of the cardiac function.

**Patients positioning:** The choice of the operating table is crucial for correct positioning; for the anterior approach a supine position with moderate Trendelenburg is preferable, while the posterior approach requires the prone positioning of the patient with complete abduction of the lower limbs, moderate flexion of the knees, careful protection against skin pressure and nerve pressure complications and monitoring of the distal vascularization.

**Intraoperative assistance:** requires experience with the instruments used in the two different phases of the procedure, including the use of some new devices to minimize bleeding, such as Acquamantis or Ultracision, and some new threadwire saws for lateral osteotomies of the sacrum. Monitoring of the anesthesiologic parameters is continuously needed, in view of possible massive bleeding occurring acutely or cardio-vascular intraoperative complications.

**Results:** Surgical time ranged from 3 to 26 hours; blood loss ranged from 2000 to 26000 mls.

The introduction of the modified Osaka technique using threadwire saw dramatically decreased both blood loss and surgical time. Intraoperative complications occurred in 9 patients, including massive bleeding and vascular lesions. Early postoperative complications were 35, most of these wound infections related to the proximity of the bowel and the prolonged surgical time. Actuarial overall survival was 67% at 10 years and local recurrence rate was about 33% with wide margins.

**Conclusions:** Favorable outcome can be achieved in patients with sacral chordomas with resection of the sacrum with wide margins. This type of surgery is complex and requires a team approach with careful pre and intraoperative assistance to minimize risks and complications.

# DRINKING RESTRICTIONS FOR PATIENTS WITH OSTEOGENT SARCOMA RECEIVING HIGH DOSE METHOTREXATE (MTX) (12 G/M<sup>2</sup>)

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Charlott Våde, Sissel Gjengedal, Svein Rian, Kjersti Stokke.

Oslo University Hospital – The Norwegian Radiumhospital

Oslo, Norway

**Background:** During 2009 and 2010 the author has mapped routines for drinking restrictions at hospitals in Scandinavia treating patients with Osteogen sarcoma receiving high dose MTX. The results showed that drinking routines varies a lot. With this background we decided to investigate literature to find out if drinking restrictions is requested for this group of patients.

**Method:** Systematic search in literature of routines for drinking restrictions to patients receiving high dose MTX and relation between MTX-values and prognosis.

**Results:** Many studies indicates a correlation between MTX plasma values, tumor response and survival. Several studies finds a correlation between peak values more than 1000 µmol/L and increased survival. Some studies do not find this correlation.

Three studies finds a correlation between good histological response and 24 hour MTX value. One study correlates 48 hour MTX value with good histological response.

Several studies concludes that hydration is important for MTX value. If hydration means intravenous fluid or includes oral intake are often unknown.

One study finds a correlation between MTX value (three courses) over 1500 µmol/L and poor histological response.

**Conclusion:** Routines for patients receiving high dose MTX varies a lot in Scandinavia. Literature shows that drinking restrictions are important for patients receiving high dose MTX. We found no evidence that patients should drink less than 600 ml/24 hour and our recommendations are:

Drinking per os:

- 1.day 600 ml (1 – 24 hour)
- 2.day 1000 ml (24 – 48 hour)
- 3.day 1000 ml (48 – 72 hour)

Delayed secretion of MTX : Free drinking

## USE OF POLYURETHANE FOAM INSIDE PLASTER CASTS TO PREVENT THE ONSET OF HEEL SORES IN THE POPULATION AT RISK. A CONTROLLED CLINICAL STUDY

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Rossana Genco<sup>1</sup>, Cristiana Forni<sup>1</sup>, Loretta Loro<sup>1</sup>, Morena Tremosini<sup>1</sup>, Sandra Mini<sup>1</sup>, Elettra Pignotti<sup>2</sup>, Ombretta Bigoni<sup>3</sup>, Giuseppe Guzzo<sup>3</sup>, Laura Bellini<sup>3</sup>, Carmela Trofa<sup>3</sup>, Anna Maria Di Cataldo<sup>3</sup>, Marilena Guzzi<sup>3</sup>

<sup>1</sup>Research Nurses, <sup>2</sup>Statistician, <sup>3</sup>Plaster cast nurses

**Aim:** The aim of this study was to test the effectiveness of polyurethane foam in contact with the heel inside a plaster cast to decrease the rate of pressure sores in the population at most risk.

**Background:** The rate of pressure sores caused by the plaster cast is reported to be 14-15% in the paediatric population, 33.3% in patients having undergone chemotherapy for bone tumours, and 43% in orthopaedic patients who already have sore skin when the cast is applied (grade 1 lesion) to the heel.

**Materials and methods:** From November 2007 to January 2009, all consecutive subjects requiring lower limb casts having undergone chemotherapy and/or presenting heel soreness received polyurethane foam in contact with the skin of the heel before applying the cast. The results were compared with those of patients with the same risk factors but were not administered the foam and were enrolled from May 2005 to August 2006.

**Results:** All together 156 patients were enrolled, 85 in the control group and 71 in the experimental group. In the experimental group 2 of the 56 patients (3.6%) patients with sore skin developed a pressure sore compared with 21 out of 49 (42.9%) of the control group without polyurethane foam ( $P < 0.0005$ ). In the experimental group 1 of the 24 patients (4.2%) patients undergoing chemotherapy developed a pressure sore compared with 18 out of 54 (33.3%) of the control group ( $P = 0.005$ ).

**Conclusions:** Placing polyurethane foam in contact with the skin of the heel inside a plaster cast prevents the formation of pressure sores.

**Importance for clinical practice:** This study provides evidence that using polyurethane foam to prevent sores even inside plaster casts in populations at most risk is a simple and cost effective strategy, and decreases the discomfort, pain and risks in these patients.

**Key words:** plaster casts, pressure sores, heel, polyurethane foam.

# COHORT STUDY OF PERIPHERAL CATHETER RELATED COMPLICATIONS AND IDENTIFICATION OF PREDICTIVE FACTORS IN A POPULATION OF ONCOLOGY-ORTHOPEDIC PATIENTS

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*Fabio D'Alessandro RN, Istituto Ortopedico Rizzoli, Bologna Italy*

**Introduction:** Peripheral venous catheters (PVC) may cause complications, specifically local.

Their management varies across health care workers and wards, and guidelines recommendations are often weak and based on experts' opinion.

**Aim:** To measure the incidence of PVCs phlebitis, occlusions, accidental removal and infiltrations and their predictive factors in an orthopaedic and oncology-orthopaedic population.

**Methods:** From may 4 2009 to 30, in an orthopedic hospital, data on patients to whom a PVC was inserted were collected: patient's and PVC characteristics, management and securing strategies, until one of the following outcomes: phlebitis, occlusion, accidental removal, infiltration or end of treatment.

**Results:** Overall, 873 patients were recruited and 139 PVCs. The following complications occurred: phlebitis 10.9%; occlusions 16.8%; accidental removals 5.8%, local infiltrations 14.4%; 648 PVCs (46.5%) were removed without complications. The risk for all complications (multivariate analysis) increased with age and for the other complications also with the administration of blood transfusions thorough PVC, irritant drugs and use >3 times/day for phlebitis; small gauge, not using PVC and surgical site infections for occlusions; positioning the PVC in the hand and fixing the PVC with the Chevron method for accidental removals; and female sex, transfusions and thromboembolic therapy for infiltrations.

**Conclusions:** The incidence of phlebitis is high compared to the gold standard of 5%. Knowing the incidence of main complications is a requirement for any improvement strategy and may favor the abandonment of useless or dangerous practices.



# EFFECTIVENESS OF THE TRANSPARENT STERILE DRESSING TO FIX THE PERIPHERAL VENOUS CATHETER (PVC) ON THE RATE OF PHLEBITIS COMPARED TO THE STANDARD DRESSING. A RANDOMIZED CONTROLLED TRIAL

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Laura Roccheggiani RN, Istituto Ortopedico Rizzoli, Italy

**Introduction:** There are studies that indicate the types of dressing that can contribute to the rate of phlebitis, infiltration and accidental removal but the results are contrasting and, in some cases, samples are too small to be meaningful.

**Aim:** To check whether the rate of the phlebitis due to peripheral venous catheter (PVC) changes by using a transparent sterile dressing made of polyurethane film to cover the insertion point of the PVC (experimental dressing) compared to a sticking plaster already in use in current practice but which does not have sterile properties (standard dressing).

*Design* Randomized controlled trial

**Participants.** 1061 PVCs (703 patients) both adults and children at a research orthopedic hospital in the north of Italy. 540 PVCs allocated to receive the experimental dressing and 521 the standard dressing.

**Results:** 96 PVCs were excluded because they caused phlebitis, 48 (9.6%) in the experimental group and 48 (10.1%) in the control group. The relative risk was 0.96 (CI. 0.697 to 1.335). Accidental removal of the PVC was greater with the sterile dressing (9.6% vs 6.3%) but the catheter removal rate at the end of treatment without complications was greater in the standard dressing group (48.9% vs 54.9%  $P=0.0503$ ). It was necessary to replace 85 PVCs because the dressing detached: 50 with sterile dressing (9.2%) and 35 with standard dressing (6.7%). The cheapest transparent sterile dressing, used in the present study, costs 32 cents each, whereas the standard one costs 9 cents.

**Conclusions:** Using sticking plasters without sterile properties (standard dressing) is not influential on the rate of phlebitis and ensures a good fix of the PVC to the skin compared with the transparent sterile dressing made of polyurethane film (experimental dressing).

# NURSING PREOPERATIVE VISIT FOR HOSPITALIZED PATIENT COMPLIANCE: VERIFICATION OF THE EFFECTIVENESS. A PILOT STUDY

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*Giovanna Gabusi*

*Istituto Ortopedico Rizzoli Bologna Italy*

Is widely known that in common imagery the unexpected or planned hospitalization in ICU (Intensive Care Unit), generates in the user and in his family a consistence emotion impact.

Feelings of anxiety, fear and stress are common manifested expression of the patient in ICU. These conditions, frequently, induce weak compliance with the assistential therapeutic project.

An assistance driven to response to the needs of single people, in order to be effective and efficient, cannot, or better, must not neglect these aspects.

The complexity of inpatient care in the ICU is not always evaluated on the basis of the stability/instability of the clinic, often, other variables can have a significant and substantial weight, such as emotional instability, relational aspects or even ethical, religious and cultural factors.

The instrument used for testing the effectiveness of the Nursing preoperative Visit for hospitalized patient compliance is the interview.

The afternoon before the operation, a nurse of Intensive Care Unit, after times agreed by telephone and the optimal time to start the interview, will visit the unit operational of the patient.

The purpose of this study is to demonstrate that the interview is a useful tool to facilitate the path to intensive care, alleviate the trauma of hospitalization, enable effective care planning and measuring adherence to therapeutic plan of care.

# LOW LEVEL LASER THERAPY IN THE TREATMENT OF ORAL MUCOSITIS ON A PAEDIATRIC HAEMATO - ONCOLOGY AND STEM CELL TRANSPLANTATION UNIT.

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V. Van de Velde <sup>1</sup>, J. De Porre <sup>1</sup>, Y.Benoit <sup>1</sup>, C. Dhooge <sup>1</sup>, R. Cauwels <sup>2</sup>

<sup>1</sup>: Dept. of Paediatric Haemato-oncology, Ghent University Hospital, Ghent, Belgium

<sup>2</sup>: Dept. of Paediatric Dentistry & Special Care, PaeCaMed-research, Dental school, Ghent University, Ghent, Belgium

**OBJECTIVE:** Despite the implementation of evidence based mouthcare guidelines, oral mucositis (OM) remains a frequently encountered and painful complication of chemotherapy.

There is an increasing evidence that low level laser irradiation can reduce the severity and duration of mucositis.

The objective of this study was to assess the effectiveness, quantitatively and qualitatively, of low level laser therapy (LLLT) for the treatment of chemotherapy induced OM in pediatric patients.

**METHOD:** When mucositis occurred, patients were treated using AlGaAs diode laser every two days until complete healing of the mucositis. Patients were evaluated for pain severity by the visual analogue scale or the faces pain scale before and immediately after LLLT. OM grade (WHO-criteria) as well as functional impairment were evaluated. Both nurses and dentists were trained to assess OM and to administer LLLT in an identical way. Data is analyzed using SPSS version 17.

**RESULTS:** From May 2009 till December 2011, 122 children, mostly with diagnosis of leukemia, lymphoma, osteosarcoma or Ewing sarcoma, treated with chemotherapy and suffering from chemotherapy-induced mucositis, were treated with LLLT. Out of these 122 patients, 23 had undergone a hematopoietic stem cell transplantation. Age ranged from 1 to 17 years.

During 300 mucositis episodes, 846 treatments with LLLT were done and 3124 lesions were treated.

Distribution of mucositis grade was : grade 0 (n=59), grade 1 (n=1181), grade 2 (n=1228), grade 3 (n=438), grade 4 (n=98) and unknown (n= 120).

Cheeks (n=828), tongue (n=640), lips (n=521), pallatum (n=259) and gums (n=233) were the most frequent sites affected.

A mean of 4 to 5 treatments were necessary to heal mucositis and to obtain overall pain relief.

For 1301 lesions there was an immediate pain relief and in 692 cases the pain remains the same. In 799 cases pain scores were missing due to noncooperation or young age of the patients or invalid scores.

**CONCLUSION:** These results demonstrate that LLLT, in addition to standard oral care can reduce pain. Four low level laser treatments per mucositis episode seem to be a realistic approach. Further research and controlled randomized trials are necessary to confirm the efficacy of LLLT and to develop more general guidelines.

CAROL HUGHES

*Royal Orthopaedic Hospital Foundation Trust, Department :Oncology, Bristol Rd South, Northfield, Birmingham*

The incidence of phantom limb pain (PLP) is variously estimated at about 70%. It is even higher when pre-amputation pain is present, so represents a significant problem in orthopaedic oncology. Conventional treatment for neuropathic pain is with the gamma-aminobutyric acid analogue (eg Gabapentin). Mirror Box Therapy can be helpful in some cases. It is thought to work by providing artificial visual feedback which “tricks” the brain into thinking it is possible to “move” the phantom limb, and to unclench it from potentially painful positions. The author will present the rationale for utilising the power of the imagination to create helpful feedback and illustrate with a case history. Could this be a useful adjunctive therapy to manage PLP?

# THE PROBLEM OF PAIN IN ORTHOPEDIC INTERVENTIONAL RADIOLOGY DURING CT-GUIDED NEEDLE BIOPSY OF BONE

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Loretta Loro RN,<sup>1</sup> Cristiana Forni RN,<sup>1</sup> Gelsomina Volpa RN,<sup>1</sup>; Elettra Pignotti PhD,<sup>2</sup> Eugenio Rimondi MD<sup>3</sup>

<sup>1</sup>Research Nurse, <sup>2</sup>Statistician, <sup>3</sup>Doctor of Medicine

**Aim:** To record the levels of pain perceived before, during and immediately after the procedure of CT-guided needle biopsy of bone, with respect to pain therapy, the harvesting site and the patient's characteristics.

**Background:** There has been a rapid increase in interventional radiology procedures in recent years but there are still few studies about pain control during these operations.

**Design:** Prospective Cohort Study

**Material and Methods:** From January 2008 to July 2010 all patients admitted to interventional radiology for CT-guided needle biopsy of bone were asked to give their consent to the collection of data with regards to the extent of pain before, during and immediately after this diagnostic procedure. The level of pain perceived was recorded by the Numeric Rating Scale.

**Results:** 282 patients were assessed. The mean level of pain before the procedure was 2.4 (SD 2.94). During the procedure the mean pain level was 6.5 (SD 3.19). The level of pain perceived 15 minutes after the procedure was 3 (SD 2.99). Comparing the pain perceived before and after the procedure, there was a mean difference of 1.27 (SD 3.20) on the scale, which is statistically significant ( $p < 0.0005$ ). The change in the level of pain before and during the procedure was not sensitive to the different sites where the CT-guided needle was placed, or the patient's gender or even the type of anesthetic used (local or systemic), but was significantly correlated with age ( $P < 0.0005$ ).

**Conclusion:** The problem of pain in interventional radiology is an important one. It is urgent to establish pain therapy/sedation protocols in patients undergoing CT-guided needle biopsy of bone regardless of the biopsy site.

**Importance for clinical practice:** All patients undergoing CT-guided needle biopsy of bone must receive effective preventive pain therapy for the test regardless of the anatomical site of the procedure.

**Key words:** Radiology, Interventional; procedure pain; Risk Factors

*Lev Shula R.N.B.A., coordinator nurse,  
The Nathional Unit of Orthopedic Oncology  
Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel.*

**Background:** Osteosarcoma of soft tissues is a malignant disease that is more common among children and teenagers than adults.

These tumors are customarily treated with neoadjuvant chemotherapy followed by excisional surgery (amputation) that involves replacement of the damaged bone with an artificial implant. On the other hand, limb-sparing procedures are associated with numerous side effects of chemotherapy and radiation. This becomes within time, to chronic .

Pediatric osteosarcoma patients are likely to develop chronic osteomyelitis requiring frequent hospitalization and multiple surgical procedures, which might cause physical and emotional disability. As a result, these patients do not experience the normative development processes of healthy teenagers and young adults.

A 27-year-old woman who had been diagnosed as having osteosarcoma of the hip at the age of 10 years, had been hospitalized 20 times over the ensuing 17 years for surgical purposes or prolonged intravenous antibiotic treatment. She also underwent chemotherapy 10 times during the same period of time.

After many years of refusing surgery in order to improve her quality of life, she now decided to undergo the procedure following many talks with the attending physician and the nurse coordinator. The planned surgery was a hip disarticulation amputation.

The surgical results were excellent, and she was optimistic and free of pain almost immediately afterwards. She is currently in a rehabilitation facility where she is undergoing treatment at an unexpectedly rapid pace She is a candidate for a place in an independent apartment community.

Limb amputation is generally considered as being an aggressive medical intervention that causes severe disability. In this case, the amputation of her limb enabled a young woman to shed a lifestyle and self-image of disability to one of positivity and strong motivation to live life to the fullest.



# ASSESSMENT OF EARLY AMBULATION IN MUSCULOSKELETAL ONCOLOGY IN PATIENTS WITH LOWER LIMB AMPUTATION AND PREDICTIVE FACTORS.

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Barbieri M, Bonetti E, Bortolotti R, Merli L, Rossi M.

**Introduction:** The survival rate of patients with bone cancer treated with amputation has been increasing over the years, determining the demand of greater attention to the needs of autonomy and quality of life of the patients. An early rehabilitation approach is necessary to reach an optimal motor performances overtime. The aim of this retrospective study is to identify the number of days required to attain autonomy for early ambulation in patients operated for lower limb amputation.

**Materials and methods:** Data collection at the Istituto Ortopedico Rizzoli (IOR) was effected using Rizzoli Computer System (SIR) and the records from Struttura Complessa di Medicina Fisica e Riabilitativa (SCMFR). Subjects were selected between the hospitalized at the IVth Clinic who received amputation of foot, leg, thigh or abdominopelvic from January 2001 to July 2011. Beginning of the physiotherapeutic treatment and attaining of early ambulation times have been recorded.

**Results:** A group of 318 subjects was identified. Patients were operated for lower limb amputation of the musculoskeletal system for oncologic diseases and for 280 of them rehabilitation was required 173 men (62%) e 107 women (38%), average age 54 years-old.

Mean times for clinical admittance from surgery corresponds to 3,8 days (average  $\pm$  3), while mean times for ambulation corresponds to 6,1 days (average  $\pm$  4). Comparing the second five-year period (2006-2011) with the first one (2001-2005), is it possible to observe a reduction of the mean time of ambulation that changes from 6,5 days (average 5) to 5,7 days (average 4). At the same time a reduction regarding the beginning of the rehabilitation was recorded, from 4,5 days (average 4) to 3,4 days (average 3).

**Conclusions:** In the post operative phase, the rehabilitation process of patients who received amputation should focus on improving their level of independence, with special regard upon the autonomy of the patient movements.

An early beginning of rehabilitation has proved to enhance an anticipation of the autonomy of movements of the patients.

Mrs K Grant, Mr P Cool, Miss G Cribb

The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust

**Introduction:** This is a prospective study analysing the effect of inpatient physiotherapy for patients who had tumour resection and surgical reconstruction.

**Methods:** Eleven subsequent patients who had a surgical reconstruction following tumour resection were admitted for inpatient physiotherapy 6 – 24 weeks after surgery (average 10 weeks).

The average age was 46 years (21 – 72 years). Nine patients had lower limb surgery and two patients had surgery to the upper limb. Four patients had metastatic bone disease and seven had a primary bone tumour. Ten patients had surgical reconstruction with an endoprosthetic replacement. The remaining patient had soft tissue reconstruction following excision of a malignant primary shoulder tumour. All patients had a TESS score on admission and discharge.

**Results:** Before physiotherapy admission, the average TESS score was 47% (14 – 73 %). Following inpatient physiotherapy the TESS score was 68% (20 – 90%). Only one patient failed to have a significant improvement in function. The average increase in score was 21% (0 - 49%). Statistical analysis using a Mann-Whitney-Wilcoxon test confirmed a significant difference at  $p=0.2\%$ .

**Discussion:** We strongly recommend inpatient physiotherapy following tumour surgery with surgical reconstruction.

## QUALITY OF LIFE AND FUNCTIONAL ABILITY IN CHILDREN AND YOUNG ADULTS AFTER MALIGNANT BONE CANCER SURGERY OF THE LEG.

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WP Bekkering, TPM. Vliet Vlieland, HM Koopman, GR Schaap, A Beishuizen, H.W. Bart Schreuder, Paul C. Jutte, RGHH Nelissen, AHM Taminiau.

Leiden University Medical Centre, Academic Medical Centre University of Amsterdam, Erasmus MC University Medical Centre - Sophia Children's Hospital, Rotterdam, Radboud University Nijmegen Medical Centre, University Medical Center Groningen, The Netherlands.

**BACKGROUND:** A great majority of osteosarcoma and Ewing-sarcoma occurs in young people under the age of 20 years. However, the average age at evaluation in most studies is 20 years or older and include mainly patients several years after their diagnosis and surgical treatment. This approach fails to address the specific issues that affect children and young people following limb ablation or salvage surgery and little is known about the impact of surgery over time or in the period immediately after the intervention.

Therefore, aim of the present study was to evaluate patients' quality of life (QoL) and functional ability; prospectively during a 2-year postoperative period and cross-sectional within 5 years after the surgery for lower-extremity bone cancer.

**METHODS:** The prospective study and a cross-sectional study were conducted in five university medical centres in the Netherlands. QoL was measured with the TNO-AZL Children's or Adult's Quality of Life Questionnaires (TACQOL and TAAQOL), the Short Form-36 (SF-36) and Bone tumour (Bt)-DUX; functional ability with the Toronto Extremity Salvage Scale (TESS), the 6-minutes walk test (6MWT) and four functional performance tests.

**RESULTS:** Forty-four patients with an average age of 14.9 (SD 4.8) years were included into the prospective study. Patients showed significant improvement on the physical dimension of QoL and functional ability. These improvements were especially seen in the first 12 months after surgery.

Eighty-one patients with a mean age of 16.9 yrs (SD 4.2) were included into the cross-sectional study. In comparison with healthy controls, patients had significantly poorer QoL.

Apart from significantly better scores for functional ability tests in the limb-salvage group, nearly no significant differences were seen for any of the outcome measures between limb ablation and salvage surgery and between male and female patients.

**CONCLUSIONS:** In the first year after bone tumour surgery, QoL and functional ability improvements are most evident. In comparison with healthy peers, patients report significantly poorer QoL. Differences at QoL and functional ability with respect to the type of surgical intervention were small.

Veldman P.I., Schreuder H.W.B., Geest van der I.C.M.

Department of Orthopedic Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands.

**Introduction:** The incidence of malignant primary bone tumours in the Netherlands is about 150 per year. The most common malignant bone tumours are osteosarcoma (35%), chondrosarcoma (30%) and Ewing's sarcoma (16%). After initial treatment patients are evaluated for many years in a protocolized follow-up program. The purpose of this follow-up program is to detect and treat local recurrence and metastasis. Existing guidelines for follow-up of patients after initial treatment of malignant bone tumours are mostly based on expert opinions.

**Objectives / aim of the study:** investigate when and how a local recurrence or metastasis has been detected in patients after initial treatment of osteosarcoma, Ewing's sarcoma or chondrosarcoma. Questions are: What is the time elapsed between the end of the initial treatment and the emergence of the local recurrence and/or metastasis? Is it detected by new complaints of the patient or did it reveal during the standard follow-up program? With the results of the study a more evidence based follow-up program may be proposed.

**Materials and Method:** To answer these questions a quantitative research has been implemented through retrospective data analysis by using a digital database, containing data of patients treated for osteosarcoma, Ewing's sarcoma or chondrosarcoma in the Radboud University Medical Centre, supplemented with research from the medical file.

**Results and Conclusions:** As research takes place up until April 2012, results and conclusions cannot be shown in this abstract but will be presented at the 13<sup>th</sup> symposium of the EMSOS Nurses Group.

# APPLYING OF HYPERTHERMIA IN LIMB SALVAGE SURGERY FOR BONE TUMOR OF EXTREMITIES

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Qing-Yu fan, Ma Boan, Zhou Yong, Zhang Minhua, Shen Wanan, Li Zhao

Presenting Author: Qing-Yu Fan

Department of Orthopedic Surgery, Tangdu Hospital, Fourth Military Medical University, Xi'an, China, 710038 - E-mail: bonetm@fmmu.edu.cn

The limb salvage process still has many unsolved problems, which remain severely limiting the long-term function of the preserved limbs. The aseptic loosening at a specified future date is a main concern. The inherent problems are related to the materials used. The anchorage of metallic parts to bone and to soft tissues is especially a poorly solved problem. For young patients, the implantation of artificial material will have to stand wear and tear for decades.

The advent of the ablation in situ has gained significant interest due to the appeal of durability of the implants.

In medicine, ablation is defined as the removal of a part of biological tissue, or killing cancerous cells by any kind of physical, chemical or other method (such as microwave, liquid nitrogen, x-ray radiation, and irreversible electroporation) .

The microwave devitalized bone was proved to have a very good potential of osteogenesis. Instead of en-bloc resection of tumor- bearing bone, only dissect it from surrounding normal tissues, then devitalize the bone segment by microwave induced hyperthermia in situ through the antenna array which are properly distributed in the tumor bulk, and finally re-strengthen the dead bone through autograft, or allograft plus prophylactic fixation of plate and screws, making its mechanical property strong enough to support the weight bearing. In this way, the structures of the adjacent natural joint were salvaged well. The function was greatly improved.

Between July 1992 to March 2009, 719 patients with malignant bone tumors of the extremities were treated using hyperthermia at the authors' institution as follows:

629 cases with high grade malignant sarcoma of extremities (mainly is osteosarcoma, second and third diagnosis are MFH, Ewing's sarcoma), 62 cases with low grade sarcomas (chondrosarcoma 42cases, adamantinoblastoma 16 cases), and 28cases with metastatic lesion. Distribution among the different ages, sexes, and places are not special compared with the reports in the literature. Before surgery, three courses of chemotherapy were given.

**Results:** The beyond 3 years survival rate was 59.1% for high-grade malignancy. Unlike carcinoma, sarcoma commonly suffered the young persons, and the metastasis appeared in lung at the period of mean 18 months after operation. (13) The life tables of event-free survival have stable plateaus beyond 3-4 years, and relapses after 3 years are infrequent. The majority of patients surviving 3 years without evidence of recurrence are probably cured. (14) The beyond 3 years survival rate was 88.7% for low-grade malignancy. For the metastatic lesions, the aim of the surgery is to relieve symptoms.

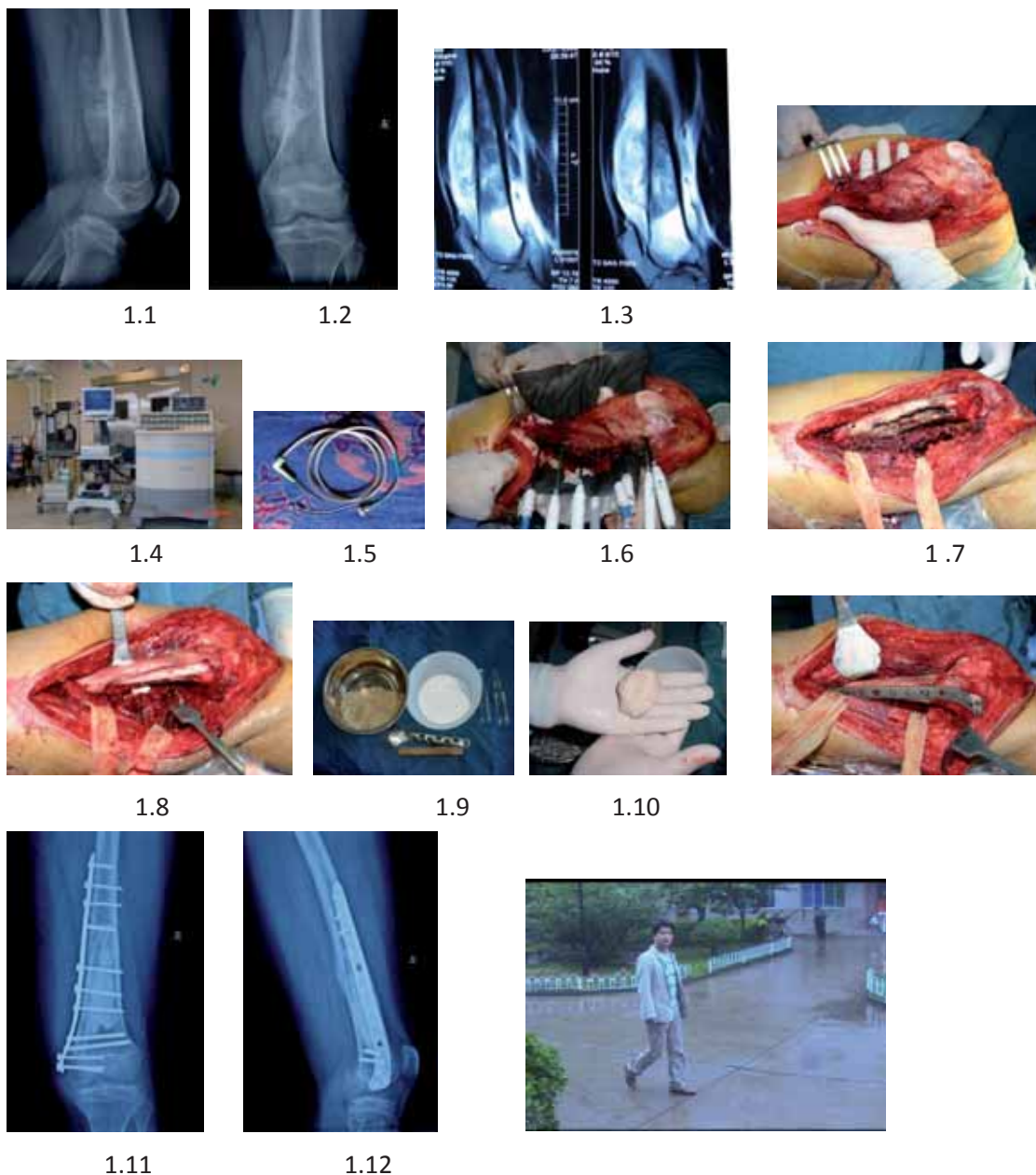
**Complications:** Local recurrence rate is 8.5%, Fracture rate is 5%. It was worse in the early stage of the study. Autograft of the fibula (even vascularized) and wearing of partial-weight bearing brace diminished the fracture rate. No one had amputation due to fracture.

Deep infection rate is 1.8%.

In majority of the patients alive, cosmetic and useful limbs were preserved. Once healing is occurred, it is durable without any further concern of the loosening. Average functional score is about 90%. Even though it is not every case that has been uniformly satisfactory, sufficient success has been achieved.

Typical cases:

# 1. Osteosarcoma in distal femur



**Fig 1: Typical procedure for osteosarcoma at distal femur.**

- 1.1-1.2: Image data shows an osteosarcoma of distal femur
- 1.3: Dissect the tumor-bearing bone from surrounding normal tissues with a safe margin.
- 1.4-1.5: Microwave generator and antenna
- 1.6: Introduce electromagnetic energy into tumor bone
- 1.7: Remove or curettage the soften tumor mass
- 1.8: Fibular bone allograft
- 1.9: The mixture material of bone chips and bone cement
- 1.20: Restore the normal shape of the femur and give a prophylactic fixation
- 1.11: X-ray film after surgery
- 1.12: Function is perfect after 11 years



## BORDERLINE CARTILAGINOUS TUMORS: BIOLOGIC POTENTIAL AND PROGNOSTIC FACTORS.

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*Irena Boulytcheva M.D.Ph.D., Alexandr Bondarev M.D., professor Nikolay Kushlinskiy., professor Anatoly Machson.  
N.N. Blokhin Cancer Research Centre, Hospital #62 - Moscow - Russia.*

The aggressive behavior of borderline cartilaginous tumors and chondrosarcoma varies from slowly growing, nonmetastasizing tumors to highly aggressive sarcomas. The modern classification identifies low grade chondrosarcomas and chondromas. Is there anything in between? Is it safe to introduce intralesional curettage for borderline lesions without compromising patient outcome? What is the best diagnostic approach and weight of morphology and immunohistochemistry in making a decision?

**Methods:** We retrospectively reviewed 350 patients with chondrosarcomas of different grades and 50 patients with chondromas from 2000 through 2011. The mean age of the patients was 38 years (range, 24-72 years) with a predilection for men (198/152) in chondrosarcomas and women (31/19) in chondromas. The minimum follow-up was 0,6 year. All patients underwent modern surgical treatment in N.N. Blokhin Cancer Research Centre and Hospital # 62, Moscow, Russia with incorporation of CT and MRI for details before and after the operation. To perform immunohistochemical study (MMP-1,-2,-9, Bcl-2, COX-2, Bax, estrogen receptors) we chose 65 cases of grade 1 chondrosarcomas and 32 borderline chondromas with aggressive radiographic, or morphologic behavior.

**Results:** The overall disease-free survival rates were similar between so called "atypical chondromas" and grade 1 chondrosarcomas. Local recurrence and metastases were rare in long bones and more common in axial skeleton. The prognostic factors, that determine the outcome were related to anatomic site, tumor size, adequacy of treatment. Multidisciplinary approach in diagnoses is mandatory. Overexpression of Bax, MMP-1 and MMP-9  $\geq 40\%$  is a marker for altered cell phenotype and more aggressive behavior of the tumor.

**Conclusions:** Local recurrence and potential metastasis are low in the group of aggressive (atypical ) chondromas and low grade (grade 1) chondrosarcomas. To better classify these lesions multidisciplinary approach is necessary. Radiographic criteria, morphology and immunohistochemistry helps to tailor less aggressive surgical procedure without compromising the results of the treatment.

D. Andreou<sup>1</sup>, A. Frings<sup>2</sup>, P.U. Tunn<sup>1</sup>, A. Leithner<sup>2</sup>

<sup>1</sup> Department of Orthopedic Oncology, Helios Klinikum Berlin-Buch, Sarcoma Center Berlin-Brandenburg, Berlin, Germany; <sup>2</sup> Department of Orthopedics and Orthopedic Surgery, Medical University of Graz, Graz, Austria

**Objectives:** Chondrosarcoma of bone rarely affects children and adolescents and there are only a few data about its course in this subgroup of patients in the literature. The objective of this study was to examine the clinical course and outcome of chondrosarcoma of bone in children and adolescents.

**Materials and methods:** 13 children and adolescents, 9 female and 4 male, with a chondrosarcoma of the pelvis (n=4), the humerus (n=3), the femur (n=2), the phalanges of the hand (n=2), the tibia (n=1) and the thoracic wall (n=1) underwent operative treatment at our institutions between 1978 and 2011. Mean patient age at diagnosis amounted to 15.2 years (range, 11 – 18 years), mean follow-up was 10.3 years (range, 0.33 – 21.25 years).

**Results:** 8 patients presented with a grade 1, 4 patients with a grade 2 and 1 patient with a grade 3 tumor. 4 patients underwent an intralesional and 9 patients a wide resection, according to the Enneking classification. No patients received chemotherapy; adjuvant radiotherapy was performed in 1 patient. 5 patients developed a local recurrence after a mean of 2.6 years (range, 0.6 – 6.5 years), following an intralesional resection in 3 cases and a wide resection in the remaining 2 patients. All 5 local recurrences were treated operatively. 1 patient with a grade 3 tumor developed lung metastases 4 years after initial diagnosis, which were also treated operatively. No patient has died of disease in follow-up.

**Conclusions:** Chondrosarcoma of bone in children and adolescents appears to have an excellent prognosis. Surgical resection without adjuvant treatment appears to be sufficient both for primary and recurrent tumors.

## INTERMEDIATE GRADE OSTEOSARCOMA AND LOW GRADE CHONDROSARCOMA ARISING IN THE SAME PATIENT: AN EXTRAORDINARY CASE IN MULTIPLE EXOSTOSIS

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Zoccali C.<sup>1</sup>, Prencipe U.<sup>1</sup>, Marolda G.<sup>1</sup>, Favale L.<sup>1</sup>, Covello R.<sup>2</sup>, Ferraresi V.<sup>3</sup>, Biagini R.<sup>1</sup>

<sup>1</sup>Division of Orthopedics, <sup>2</sup>Division of Pathology, <sup>3</sup>Division of Medical Oncology A,  
Regina Elena National Cancer Institute  
Rome - ITALY

**Background:** Hereditary multiple exostosis is an autosomal dominant skeletal disorder characterized by the development of multiple osteochondromas that can result in orthopedic deformities. In the major of cases a positive familiar history is present but several cases are ex novo. The most serious complication of HME is the transformation of an osteochondroma in chondrosarcoma that is of peripheral type in 95% of the cases. The frequency of malignant transformation is reported to vary from 1% to 25%, being non consensus in literature. Osteosarcoma presents a prevalence of about 2-3 cases/million population/year. No case of association between osteosarcoma and chondrosarcoma are found in literature.

**Case report:** A 50 years old Caucasian lady, affected by hereditary multiple exostosis, showed up at our department because of the presence of a multinodular recurrence of a low chondrosarcoma in the posterior aspect of the sacrum arisen two years after a intralesional resection. A sacral resection was scheduled but an apparently not significant uptake of 2 cm in diameter was found at preoperative CT-PET into the vertebral body of D12. The CT guided biopsy revealed a diagnosis of a intermediate grade osteosarcoma. Taking into account the concomitant presence of the two tumors, it was decided to first treat the major aggressive OS; neoadjuvant chemotherapy was excluded basing on the intermediate grade of the OS and the necessity to avoid a long delay before the treatment of the multinodular recurrence of the sacral chondrosarcoma. An en bloc vertebrectomy was performed. Histopathology on the vertebral specimen evidenced a low grade OS so any other systemic therapy was considered not useful. Sacral resection was done three months later when the patient was sufficiently healthy to undergo to a second important operation. A multinodular recurrence of a low grade chondrosarcoma was found in the sacrum. At one year of follow-up she is alive and without evidence of disease.

**Conclusion:** The clinical case we presented is apparently the first reported in literature of a patient simultaneously affected by a chondrosarcoma and an Osteosarcoma. When a hereditary syndrome is present every suspected finding has to be investigated to exclude further concomitant tumors.

# EXTRASKELETAL MIXOID CHONDROSARCOMA OF THE LIMBS: THE EXPERIENCE OF DEPARTMENT ORTHOPEDIC ONCOLOGY OF FLORENCE

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Beltrami G, Frenos F, Franchi A\*, Scoccianti G, Matera D, Caff G, Campanacci DA, Capanna R

Orthopaedic Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, CTO Largo Palagi 1, 50139 Firenze, Italy

\* Department of Human Pathology and Oncology, University of Florence Medical School, Florence, Italy.

**BACKGROUND:** Extraskeletal myxoid chondrosarcoma is a rare soft tissue neoplasm, high grade and affecting young adults. The dial of our paper is to analyze the biological characteristics and clinical behavior of our cases.

**METHODS:** From the overall data base of 1210 soft tissue sarcoma cases treated at Department of Orthopedic Oncology of Florence we analyzed all the extraskeletal myxoid chondrosarcoma cases. They were 15 patients (10 males and five females), treated from 2001 to 2011, with an average follow-up of 47 months (range 6-153). The mean age at diagnosis was 62 years (range 37-83), lower limb was involved in 11 cases (73%, 5 thighs and 5 legs, 1 pelvic girdle), upper limb in four cases (one girdle and three distal of the elbow). According to WHO, any histological grading system was applied, but all the cases were rated as "atypical" high grade.

All the patients have been reviewed, considering histological, clinical, oncological and functional results.

**RESULTS:** All patients but one were treated by limb sparing surgery; one was primarily amputated due to local extra-compartmental extension. Surgical margins were rated as wide in 10 patients, marginal in three, radical in two. In three cases adjuvant radiation therapy was associated, while chemotherapy was employed only in one case. Three main complications were found: one deep venous thrombosis and two complication related to radiationtherapy (one scar slough with secondary infection and one late bone fracture). At follow up, no secondary amputation were performed and no patient developed local recurrence or metastases.

**CONCLUSIONS:** In our experience, extraskeletal mixoid chondrosarcomas are locally aggressive tumors and conservative surgery with wide margins is recommended, while adjuvant radiationtherapy has to be considered if marginal excision is proved. In our cases with average four years follow up, no systemic progression have been observed, but a longer follow up is necessary because late pulmonary metastasis have been described.

# DETECTION OF HEY1-NCOA2 FUSION BY FLUORESCENCE IN SITU HYBRIDIZATION IN FORMALIN-FIXED, PARAFFIN-EMBEDDED TISSUES AS A POSSIBLE DEFINING DIAGNOSTIC TOOL IN MESENCHYMAL CHONDROSARCOMA

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Robert Nakayama 1 robert@a2.keio.jp - Jiro Ogino 3 - Michiro Susa 1 - Itsuo Watanabe 1 - Keisuke Horiuchi 1 - Ukei Anazawa 4 - Yoshiaki Toyama 1 - Hideo Morioka 1 - Makio Mukai 2 - Tadashi Hasegawa 3

<sup>1</sup>Department of Orthopaedic Surgery and <sup>2</sup>Department of Pathology, School of Medicine, Keio University, Tokyo, Japan

<sup>3</sup>Department of Surgical Pathology, School of Medicine, Sapporo Medical University, Sapporo, Japan

<sup>4</sup> Department of Orthopaedic Surgery, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan

**Objectives:** Mesenchymal chondrosarcoma is an extremely rare subtype of chondrosarcoma. It typically shows a mixture of Ewing-like small round cell area and islands of chondroid matrix, however, histological diagnosis of this tumor is often difficult since the proportion of the two components vary in each case. Recently a tumor specific fusion gene, *HEY1-NCOA2*, has been identified by Wang *et al.* (Genes Chromosomes Cancer. 2012), and this finding should improve the pathological diagnosis and promote understanding of mechanisms underlying pathogenesis of this tumor. In order to validate the efficacy of the Fluorescence In Situ Hybridization (FISH) detecting *HEY1-NCOA2*, eight cases of mesenchymal chondrosarcomas were analyzed.

**Materials and Methods:** A query of our database yielded eight cases histologically diagnosed as mesenchymal chondrosarcoma. Formalin-fixed paraffin-embedded (FFPE) sections were pretreated and dual-color FISH was performed using two probes detecting both *HEY1* and *NCOA2*.

**Results:** There were four males and four females, and the age at diagnosis ranged from 14 to 42 years old (average 26.9). Four patients developed their disease in the bone, (axis (n=2), rib (n=1), fibula (n=1)), while four patients had them in the soft tissue (lower limb (n=2), sacral meninx (n=1), abdominal wall (n=1)). Fusion signals were detected in all six tumors in which the FISH signals were positive. There were two cases negative of FISH signal, one due to decalcification of the tumor, and the other one due to inadequate volume of tumor in the specimen.

**Conclusions:** We were able to validate the efficacy of the molecular diagnosis by FISH detecting *HEY1-NCOA2* in diagnosis of mesenchymal chondrosarcoma. In addition to the results by Wang *et al.*, the sensitivity of FISH detecting *HEY1-NCOA2* is 100% in tumors with a definitive diagnosis and adequate specimen showing positive FISH signals. This tool should be useful especially when the tumor has little chondroid matrix presenting as a pure round cell sarcoma. Since mesenchymal chondrosarcoma usually present as a hard calcified mass, tumor sampling for FISH before decalcification should be considered when this rare sarcoma is suspected.

M. Rocca, M. Salone, °P. Ruggieri, °A. Angelini, A. Briccoli

General Surgery and °Orthopaedic Oncology – Rizzoli Orthopaedic Institute – Bologna, Italy

**Objectives:** To present our experience in the diagnosis and surgical treatment of chest wall chondrosarcoma (CS) which, although a rare entity, is the most common malignant tumor of the chest wall.

**Materials and Methods:** Over the last 20 years, 34 patients with CS of the chest wall were surgically treated at the Rizzoli Orthopaedic Institute in Bologna. There were 25 men and 9 women ranging in age from 23 to 74 years. The median follow-up period was 44 months. The tumor was located in ribs only in 20 patients, in the sternum and ribs in 9, in sternum only in 4, and in the ribs and spine in one. The most frequent histological variety was central with 27 observations. 28 out of 34 were high grade CS, 5 of them had been previously submitted to surgery in other hospital and developed a local recurrence. CT scan with intravenous contrast is the gold standard study for diagnosis. An ultrasound study of the tumor was performed to analyze the superficial surgical margins and to identify the presence of micronodules in recurred cases.

**Results:** Reconstruction using cadaveric fascia lata or Marlex mesh was combined with mouldable metal plates to prevent flail chest in 19 patients, resection alone was performed in 8 patients, and a muscular flap was used in 7 patients. Five-year overall and disease-free survivals were 83% and 67%, respectively. One operative death occurred, another required temporary tracheostomy, one patient developed a fistula during post-operative chemotherapy (the only case of dedifferentiated CS). Survival was statistically higher in patients primarily treated at our institution than patients treated for recurrence. In 18 patients treated with wide excision and reconstruction of the chest wall, the postoperative respiratory function test result (at 6 months) was 10% less than the preoperative one.

**Conclusions:** Surgical treatment involving wide exeresis is mandatory. In wide excisions, the reconstruction method with fascia lata or marlex associated to metal plates is a reliable and reproducible surgical technique.



## RESULTS OF THE TREATMENT OF PEDIATRIC CHONDROSARCOMA

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*D.B. Khestanov, A.Z. Dzampaev, N.M. Ivanova, M.D. Aliev*

*Institute Pediatric Oncology and Hematology Russian Cancer Research Center, Moscow*

**Purpose:** To investigate prognostic factors, biological behavior of tumors and individual features of pediatric patients with chondrosarcoma (CS). To improve survival of the children with CS by using of PHT and surgery.

**Materials and methods:** In our study were included 77 children. Median age was 12 years (range, 3 to 17) with CS treated in IPOH RCRC from February 1981 to February 2010. Boys were 38 (49,4%), girls — 39 (50,6%). Male-female ratio was 1:1. Localized disease was in 62 (80,5%) pts, metastatic — 15 (19,5%). Lung metastasis were observed in 13 (16,9%) cases, combined metastasis — 2 (2,6%). We used combined approach in the treatment of CS grade (G) II and III: aggressive PHT with doxorubicin, CDDP, ifosfamide, etoposide, HD MTX and surgery. Patients with CS GI treated with surgery only.

**Results:** Use of aggressive PHT improve limb salvage rate from 30% to 48,4%, advance 5-year overall survival from 63,4% to 75,1%, 5-year DFS from 50,6% to 74,4%, improve radiological response rate (PR+CR) from 57,2% to 87,5%. Two-years DFS in pts treated with surgery was 80,5% compared with 23,8% in pts without surgery ( $p<0,05$ ). Five-year DFS in pts with histological response GIV was 100%, GIII— 88,4%, GII — 52,5%, GI— 48% ( $p<0,05$ ).

**Conclusion:** Use of aggressive PHT in children with CS GIII and GII improve 5-y DFS to 74,4%. Main prognostic factors were duration of anamnesis, primary site, grade of tumor, radiological and histological response.

Mr S. Evans<sup>1</sup> MBChB MRCS. St4 Trauma and Orthopaedics  
 Ms S. Chaudhry<sup>1</sup> MBChB MRCS. SpR Trauma and Orthopaedics  
 Mr M. Boffano<sup>1</sup> Senior Tumour Fellow  
 Mr L. Jeys FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon  
 Mr A. Abudu FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon  
 Mr R. Tillman FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon  
 Mr S. Carter FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon  
 Mr R. Grimer FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon  
<sup>1</sup> Royal Orthopaedic Hospital, Birmingham, Birmingham, UK.  
 Lead author: Mr. Scott Evans.  
 Email: drscottbevans@yahoo.co.uk

Royal Orthopaedic Hospital, Birmingham

**Aim:** Identify patients treated at our centre with synovial chondromatosis that subsequently developed into a synovial chondrosarcoma.

**Methods:** Retrospective review of a prospectively collected database. Patient demographics recorded along with site of primary synovial chondromatosis. From this, details of those patients who subsequently developed synovial chondrosarcoma were collected.

**Results:** 77 patients identified. 45 male, 32 female. Mean age at presentation with synovial chondromatosis 49.3 years. All referred to our unit with pain, swelling or loss of function to the affected area; 30 knees, 21 hips, 6 shoulders, 5 fingers, 5 feet, 5 elbows, 2 hands, 2 wrists, 1 ankle. Of the 77 patients, 4 (5.2%) went on to develop synovial chondrosarcoma; 3 around the hip, 1 around the knee. The median time from original diagnosis of synovial chondromatosis to malignant transformation was 11 years (range 2-41). The single knee patient was managed with an above knee amputation, but developed lung metastases 32 months after the amputation and died 18 months later. Of the 3 hip patients, 1 was managed with a hind-quarter amputation and at last follow-up, 12 years post-surgery, was doing well with no local recurrence or lung metastases. Unfortunately, the 2 other patients who developed synovial chondrosarcoma around the hip had large, aggressive tumours. Both had debulking and total hip arthroplasty prior to developing lung metastases within 18 months of these palliative procedures.

**Discussion:** Chondrosarcoma arising in synovial chondromatosis is extremely rare with most patients having had a prolonged history of synovial chondromatosis. In both conditions (synovial chondromatosis and chondrosarcoma arising in synovial chondromatosis) the clinical presentation is similar, namely pain, swelling, loss of range of motion, and multiple previous surgical procedures. The diagnosis should be based on the histologic findings. Reports suggest a 5% prevalence of malignant transformation in synovial chondromatosis and our study would confirm this.

## DELAYED DIAGNOSIS OF CLEAR CELL CHONDROSARCOMA AFTER TOTAL HIP REPLACEMENT - A RARE ENTITY ENCOUNTERED IN COMMON SURGERY

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LISKA Franz

University Hospital Rechts der Isar Munich

Clear cell chondrosarcoma (CCCS) is a rare subtype of chondrosarcoma. Besides mesenchymal, myxoid and dedifferentiated types of chondrosarcoma the CCCS can be found in less than 10 percent of the heterogenous group of chondrosarcomas in addition to central, peripheral and periosteal/juxtacortical chondrosarcomas. Clear cell chondrosarcoma accounts for approximately 2% of all chondrosarcoma and is a rare low-grade variant of this entity. Nevertheless, marginal or incomplete excisions are associated with a 70 percent or higher recurrence rate. Metastases may develop and the overall mortality rate is up to 15 percent.

We report the case of a young female patient who received a total hip replacement due to pain in her left hip joint that was diagnosed as degenerative arthritis. A CCCS in the femoral head had not been detected at that time. Subsequently a periprosthetic relapse of CCCS close to the former femoral osteotomy occurred. Although a biopsy of the periprosthetic tumor had been taken for histologic analysis, the recurrence of CCCS remained misdiagnosed for a long time due to the rare histopathologic morphology. Finally revision surgery with wide tumor resection and reconstruction using a modular megaimplant (proximal femur replacement) had to be performed. We report the case of a periprosthetic CCCS of the proximal femur. Relevant facts of this rare entity regarding pathogenesis, treatment and differential diagnoses will be discussed.

Benini S. \*, Cocchi S. \*, Gamberi G. \*, Magagnoli G. §, Picci P. §, Ruggieri P. °, Gambarotti M. \*, Alberghini M. \*

\* Department of Pathology, Istituto Ortopedico Rizzoli, Bologna, Italy § Department of Experimental Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy, °Department of Orthopaedic Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy.

**INTRODUCTION:** Extraskeletal myxoid chondrosarcoma (EMC) is a malignant neoplasm histologically characterized by an abundant myxoid matrix and malignant chondroblast-like cells arranged in cords or clusters with eosinophilic cytoplasm. It is a rare mesenchymal tumor occurring in soft tissues and rarely in the bone accounting for less than 3% of soft tissue sarcomas. Most cases of EMC harbor the reciprocal chromosomal translocation t(9;22)(q22;q12) and the resultant fused gene EWSR1-NR4A3. A second, less common, cytogenetic subgroup of EMC is characterized by the presence of a t(9;17)(q22;q11) involving the fusion between gene NR4A3 and TAF2N. Other less frequent fusion variants of the NR4A3 gene, TCF12-NR4A3 and TFG-NR4A3 identified in a single case each, are associated with t(9;15)(q22;q21) and t(9;3)(q22;q12) respectively.

**METHODS:** The samples from patients with EMC were examined for the presence of EWSR1-NR4A3, NR4A3-TAF2N and TCF12-NR4A3 transcripts by using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) on frozen and paraffin embedded tissues. Fluorescence in Situ Hybridization (FISH) was performed to analyze the EWSR1 gene rearrangement on paraffin embedded tissue in all that samples negative for the fusion transcripts detected.

**RESULTS:** A total of thirty-eight patients with a diagnosis of EMC were characterized by molecular analyses. Chromosomal aberration was found in thirty-two samples (84% of all samples), five (13%) were negative and one was considered not evaluable. The fusion transcripts were detected in twenty-five samples by RT-PCR of which nineteen resulted positive for EWSR1-NR4A3 and seven for NR4A3-TAF2N. The presence of EWSR1 gene rearrangement was detected by FISH in seven samples resulting negative for all fusion transcripts detected by RT-PCR.

**CONCLUSIONS:** The combination of RT-PCR and FISH on frozen and paraffin embedded tissue is a sensitive and specific method for molecular detection of recurrent translocations and is an important ancillary method to establish the diagnosis of EMC.

# PERIPHERAL CHONDROSARCOMA (PCS):DIAGNOSIS AND TREATMENT OF 91 CONSECUTIVE CASES.

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The experience of the G.Pini Orthopaedic Institute in Milan from 1957 to 2010

\*S.Mapelli, P.A.Daolio, F.Lazzaro, R.Zorzi, P.Zacconi, S.Bastoni,

^E.Armiraglio, "E.Ferri, °F.Giardina, °M.S.Bartoli.

\*Orthopaedic Oncology Department; ^ Pathology Department; "Radiology Department.

Gaetano Pini Orthopaedic Institute – Milan – Italy.

°Course of Specialization in Orthopaedics - University of Milan.

**Objective:** PCS is a rare malignant neoplasm that require a very long follow-up for prognostic evaluation. For this reason there are few good and reliable studies in the literature. The purpose of the Authors is to give their contribution to these studies revising the complete consecutive series of the 91 PCS that occurred in the Orthopaedic Oncology Unit till now. **Materials and methods.** The pathological, radiological and surgical files of the patients that were registered in the Unit for a PCS from 1957 to 1984 were already revised by a team including a surgeon, a radiologist and a pathologist; the data were presented in the national congress of the S.I.O.T. in 1988. The files of the successive patients, from 1985 to 2010, are now revised and analyzed, for a total number of 91 cases.

**Results:** The second, third and fourth decades of life are the most affected; the ratio male:female is 2:1; the most frequent site of localization is the pelvis followed by the proximal femur and proximal humerus but also proximal tibia, spine, scapula and ribs are affected. In 80% of the cases there is an evident mass while pain is present in 2/3 of the patients and ¼ of them have a functional impairment. The mean duration of symptoms is 4 years. The preexisting exostosis was evident radiologically in the 70% of the cases, macroscopically in the 36% and histologically in the 17%. All the patients had a surgical treatment; 9 had an amputation, 39 a simple resection without reconstruction and 43 a resection-reconstruction with bone grafts (37) or prosthesis (6). The oncological results prove 54 patients NED and CDF, 11 NED2, 2 AWD, 18 DOD and 6 LOST. The recurrences occurred in 1/3 of the patients for a total number of 50 operations because some patient had 2 or more recurrences. Progression in malignancy was found in 10 cases (30%). The analysis of the complications show 5 deep infections, 4 mechanical failures, 3 neurological palsy and 2 vascular damages.

**Conclusions:** PCS is a rare tumor generally secondary to a preexisting exostosis; the malignant transformation of an exostosis is rare (about 1%); PCS is generally a low grade tumor and grade I PCS does not metastatize without upgrade in malignancy; wide resection is a standard indication for all cases but it can be very difficult to perform in wide lesions; the incidence of the recurrences is related to correct surgical margins more than histological grading, marginal margins has an high risk of local recurrence; recurrence can be very late and very long follow-up is required; the complete resection of the recurrences can allow very long free survival; recurrences in the trunk can become inoperable and cause death; metastases are rare.

Spinelli MS<sup>1</sup>, Graci C<sup>1</sup>, Perisano C<sup>1</sup>, Fadda G<sup>2</sup>, Rossi ED<sup>2</sup>, Valenzi E<sup>1</sup>, Di Giacomo G<sup>1</sup>, Ricciardella ML<sup>1</sup>, Falcone G<sup>3</sup>, Rosa MA<sup>4</sup>, Maccauro G<sup>1</sup>.

<sup>1</sup>Department of Orthopaedics and Traumatology, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

<sup>2</sup>Division of Anatomic Pathology and Histology, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

<sup>3</sup>Villa Valeria Clinic, Rome, Italy

<sup>4</sup>Department of Orthopaedics and Traumatology, Messina, Italy

**Objective:** In contrast to normal cartilage, which is avascular, angiogenesis is characteristic of cartilage tumors. The goal of this study was to evaluate the diagnostic relevance of the expression of growth factors in cartilaginous tumors and to investigate on the possible correlation with grade, local recurrence, metastatic potential, and survival.

**Material and Methods:** Expression of VEGF, PDGF, FGF1, TGFbeta2, TNFalpha, Ki-67, and p53 was analyzed in 29 cases of benign and malignant cartilaginous tumors, including 8 cases of hand tumors, using radiographic, histological and immunohistochemical studies.

**Results:** Immunohistochemistry revealed a high correlation between grading and VEGF-positive staining (P=0.001). In addition, a correlation with local recurrence was found in cases with a positive expression of Ki-67 (P=0.035), TGFbeta (P=0.007), PDGF (P=0.007), and p53 (P=0.0455), with a time-related association. These data suggest a progressive modification in the biologic behavior of malignant cartilaginous tumors.

**Conclusion:** VEGF could be used as a marker in the preoperative surgical assessment of chondrosarcoma. New therapeutic strategies could be considered for VEGF-positive cases. The evidence in cartilaginous tumor of the hand shows a specific model of tumour progression in which VEGF expression should be the first stadium of the tumour aggressiveness, and the following PDGF, TGF 2 expression should be accompanied with a morphological outline worsening. It is important to remember that the cellular polymorphism typical of the cartilaginous tumours does not allow the application of an only oncogenesis model.

# DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING (DCE MRI) IN CHONDRAL BONE TUMOURS

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Tiziana Robba, Maurizio Stratta, Valeria Clementi\*, Alessandra Gallo, Guido Regis, Raimondo Piana\*\*, Gian Carlo Gino\*\*, Alessandra Linari\*\*\*, Carlo Faletti

\* GE Health Care Medical System

\*\* Chirurgia Oncologica e Ricostruttiva, AO C.T.O-M. Adelaide di Torino

\*\*\* Servizio di Anatomia Patologica, AO OIRM-S. Anna di Torino

**Objective:** to investigate the role of Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE MRI) in bone tumours with chondral matrix.

**Materials and Methods:** in the period December 2010-September 2011 we performed DCE MRI in 14 patients with a chondral tumour of the bone. The contrast-media (gadobenate dimeglumine 0.5 M) was injected with flow 2.5 ml/ml by automatic injector, during multiphase acquisition of Liver Acquisition with Volume Acquisition (LAVA) or Spoiled Gradient Recall (SPGR) sequences (temporal resolution: 5'') depending on the coil used. Signal-intensity curves were obtained putting a Region Of Interest (ROI) on the largest areas of contrast-enhancement of each tumour. The start of tumoral enhancement was measured and classified into early (within 10'' after arterial enhancement), delayed (between 10''-2 ') and late (after 2'). The results were correlated with the pathological data.

**Results:** in two enchondroma the start of tumoral enhancement was late, while in one osteochondroma was delayed. It was late in a case of uncertain diagnosis (enchondroma/chondrosarcoma G1). In case of G1/G2 chondral tumours the start of tumoral enhancement was early in three patients and delayed in one case. In the remaining cases of G2 and G3 tumours the STE was always early.

**Conclusions:** the biggest limitation of our study is the small number of patients, especially of enchondroma. When the start of tumoral enhancement is late, a chondrosarcoma should be excluded, whilst an early start of tumoral enhancement should be indicative for malignancy. However in our study the start of tumoral enhancement seems to be not useful to predict the grading of the chondrosarcoma.



Y. Khan, S.A. Hanna, P. Whittingham-Jones, M.D. Sewell, R.C. Pollock, J.A. Skinner, A. Saifuddin, A. Flanagan, S.R. Cannon, T.W.R. Briggs

**Keywords:** Chondrosarcoma; Intralesional curettage; Polymethylmethacrylate cement e PMMA; Musculoskeletal Tumour Society Score e MSTs; Local recurrence

**Introduction:** Chondrosarcoma is the second most commonly occurring primary malignant bone tumour, with a peak incidence between the fourth and seventh decades of life. These tumors were first described as a separate entity by Phemister in 1930. In adults, the pelvis, ribs, shoulder girdle, femur, and humerus are mainly affected, while in children, facial bones and the knee region are the main sites. Authors link the prognosis to tumor size, anatomical location, and most importantly, histological grade. In this paper, we examine the oncological and functional outcomes of intralesional curettage and cementation as a treatment strategy low-grade chondrosarcoma of long bones.

**Background:** Different treatment strategies for low-grade chondrosarcomas are reported in the literature with variable outcomes. The aim of this study was to assess the oncological and functional outcomes associated with intralesional curettage and cementation of the lesion as a treatment strategy.

**Patients and methods:** We performed a retrospective review of 39 consecutive patients with intramedullary low-grade chondrosarcoma of long bones treated by intralesional curettage and cementation at our institution between 1999 and 2005.

**Results:** There were 10 males and 29 females with a mean age of 55.5 years and a mean follow-up of 5.1 years. Local recurrence occurred in two patients (5%) within the first two years following index surgery. Both were treated by re-curettage and cementation of the resultant defects. A second local recurrence developed a year later in one of these two patients, for which a further curettage followed by local liquid nitrogen treatment was performed. Overall, there were no cases of post-operative complications or metastases. The patients were assessed using the Musculoskeletal Tumour Society scoring system (MSTS) to determine limb function. The average score achieved was 94%.

**Conclusion:** Intralesional curettage is an effective treatment strategy for low-grade intramedullary chondrosarcoma of long bones, with excellent oncological and functional results. Careful case selection with stringent clinical and radiographic follow-up is recommended.

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## TREATMENT RESULTS OF MESENCHYMAL CHONDROSARCOMA

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Diedkov A.G., Klymnyuk G.I.

National Cancer Institute, Kiev, Ukraine

**Introduction:** Mesenchymal chondrosarcoma (MC) differs from classical chondrosarcoma uncommon, aggressive clinical course, a penchant for late recurrence and lung metastasis and occurs usually in young patients. Histologically characterized by occurrence to changeable amount of differentiated cartilaginous matrix mixed with undifferentiated small round cells. Although at the present moment there is no standart treatment of MC, most surgeons use a radical tumor resection. Effective of adjuvant chemotherapy or radiation therapy as an adjunct to surgical treatment at the present time is also not defined.

**Purpose:** Show the treatment results in comparison with the MC complex treatment and only surgical treatment.

**Materials and Methods:** Treatment result of 29 patients with MC of bones. The tumor localised in the pelvis - 4, in the long bones of the lower limb - 22, in the humerus - 3 patient treated at the institute from 1999 to 2010. Mean age - 31.1 years. Depending on the method of treatment, patients were divided into 2 groups: a group with complex treatment (treatment protocol ISG/SSG I and SSG XIV for osteosarcomas) to 11 patients and a group with only surgery treatment, 18 patients. Medium follow-up term was 54.2 and 68.4 months. Tumor response to neoadjuvant treatment was estimated decrease in tumor size and degree of tumor necrosis according to Huvos. All pelvic localization used in the neoadjuvant mode intraarterial cisplatin. Survival was studied by Kaplan-Maier.

**Results:** Surgical treatment in the form of general radical resection was performed in 27 patients, including the reconstruction of the defect endoprosthesis - 25, resection without reconstruction of the pelvis (internal hemipelvectomy type-1) - 2. Two patients with pelvic localization refused surgical treatment, they completed radiation therapy at a dose of 55 Gy. Of the 11 patients with complex treatment of clinical tumor response to neoadjuvant therapy was observed in all patients in the form of reduced pain and stabilization of tumor size. Medical pathomorphosis was in 2 patients (18.2%) as 3-rd degree to Huvos (greater than 90% necrosis), the rest - 1st and 2-nd degree. Reduction of the tumor were observed in any of the patients with complex treatment. In this group of patients with local recurrence was detected in 1 (9.1%) patients and in 3 (27.3%) – lungs metastases. In the group with surgical treatment of local recurrence was in 1 (5.5%) and metastasis in 8 (44.4%) patients. Total deaths 7 (24.13%) patients: 3 - in the group with complex treatment, 4 - with surgery treatment, on the progression of the disease. Relapse-free survival value in the group with complex treatment was higher - 56.8% compared with surgical treatment of -39,2% ( $p > 0,05$ ), though, no significant differences.

**Conclusions:** The chemotherapy in the treatment of MC in combination with surgery can achieve better results of survival, but the main treatment is surgical. Further progress in the treatment of MC is development of criteria for individualizing treatment strategy, depending on prognostic factors.

Lesenský J., Matějovský, Z., Kofránek I.

Orthopedic Clinic 1<sup>st</sup> Medical School, Charles University, Teaching Hospital Bulovka, Prague, Czech Republic

**Introduction/objective:** Even though solitary enchondromas (ECH) a rather frequent bone hamartomas, that account for the most benign tumors of the hand, their malignant counterpart in these locations is a surprisingly rare occurrence. They account only for approximately 2% of all chondrosarcomas (CHSA) of the body. Differences between central and acral (hand and feet) CHSA are well known. However the biological behaviour of the latter is still somewhat unclear and its metastatic potential is often doubted. Hence is often treated with intralesional curettage with little or no concern for distant metastases. We therefore concluded a comprehensive retrospective study with emphasis on posting a solid recommendations on how to treat these conditions.

**Materials & methods:** We reviewed charts of all patients operated in our clinic from 1965 till today and found total no. of 42 patients treated for acral CHSA. We primarily excluded all patients with incomplete charts and history less than 2 years so that a sufficient follow-up can be part of a standard. Tumors originated in distal forearm or lower leg with extension to periphery were not included as well as CHSA arising from soft tissue. Also patients with mesenchymal, dedifferentiated and clear cell chondrosarcomas were not included as they have a different biological behaviour. We included only patients with diagnosis of classical GI-GIII CHSA according to classification system by Evans.

**Results:** For 31 patients all demographic data, clinical history, histology, surgery protocols and outpatient clinic visits were available. Of these patients 22 had tumor in hand and 8 below the ankle. Most common location was the 3rd and 5th ray of the hand. Men and female were equally affected. Patients were elderly in general – mean age at the time of diagnosis was 50,1 years (6y to 87y) with peak incidence in 7th decade. The most common presenting symptom was a bulge (n=21), that was enlarging for a relatively long time (40,7 months in average) before the patients sought medical attention. One patient had a history of a slowly growing deformity for over 25 years (case 17). Pain was an inconsistent symptom that occurred only in 5 patients with the bulge and 2 patients had pain only. Few cases manifested as a pathological fracture (n=5). Tumors in the foot were more likely to be HG (75% were either GII or GIII), than those in the hand. Most majority of CHSA in our series were secondary. The most frequent underlying condition was enchondroma (ECH): n=20 (in 5 cases associated with Olliere disease and in 1 case with Maffucci sy.), followed by osteochondroma (OCH): n=3, and synovial chondromatosis (SCH) in 1 case. Only 5 patients suffered from primary chondrosarcoma. The treatment was always surgical. Four patients (13,8%) developed distant pulmonary metastases that were fatal for two of them, one patient died of unrelated causes and one patient is alive with disease.

The statistical analysis suggested that only 2 groups of CHSA should be distinguished in these settings : low grade (LG) group for GI CHSA and high grade (HG) group for the rest (GII,GIII). Patients with LG CHSA tend to be younger (40,6y vs 58,2y) and, except for one patient, were all primarily treated by intralesional surgery (91,7%). Nine of these patients (81%) suffered local recurrence (LR) (4 of them multiple) at an average of 131 months since primary surgery. Seven of them underwent ablative surgery later on and only two of them were cured after additional intralesional surgery. All of our four cases with multiple LR relapsed in a higher grade than the primary tumor - up to GIII in three cases. Two of these patients developed distant pulmonary metastases.

On the other hand 63,15% of patients with HG CHSA had an ablative surgery as a primary treatment. Only four of them had an intralesional surgery, which was always followed by LR at an average of 5,75 months. We did not encounter a single LR after primary ablative surgery, nevertheless two patients developed distant pulmonary metastases despite good local control.

**Discussion:** Our study shows, that the behaviour of acral CHSA is not as benign as generally believed and successful treatment requires careful planning. For LG CHSA of the hand and feet, intralesional surgery is widely accepted and despite the high rate of LR in our series, we believe this is still a treatment of choice. Especially because it is also rather difficult to differ GI lesion from an active enchondroma and the diagnosis is often done only retrospectively. However in case of a LR, more aggressive approach should be taken in consideration as the risk of having a HG CHSA raises with every recurrence.

For GII-III CHSA on the other hand, intralesional surgery is to be avoided. In these cases LR is constant and the potential of evolving into a fatal metastatic disease is substantial. For such tumors we recommend primarily block resection with structural autograft reconstruction wherever possible. The functional result after such reconstruction can be acceptable even in extreme cases as will be presented in case reports. The temptation of performing an IL surgery in an effort to achieve a better functional result should be resisted. As a matter of fact, usually an even more aggressive surgery is later needed to treat the recurrent tumor.

The fact, that most of these tumors in our series were secondary to a previously benign condition suggests that chondromatous lesions should be followed more carefully with respect to this. Also the higher age of patients with GII-III CHSa supports the idea, that the chondromatous tumors have a potential to progress slowly into higher grades. Therefore in case of any clinical suspicion, an early active approach is advocated. Feet were more likely to harbour a HG CHSa probably because in this location they can grow longer unnoticed.

Distant metastases developed only in patients with HG lesions, nevertheless one patient with Olliere disease had already been treated for CHSa of the femur and the source of these metastases is more likely to origin from there.

Matějovský, Z., Lesenský J., Kofránek I.

Orthopedic Clinic 1<sup>st</sup> Medical School, Charles University, Teaching Hospital Bulovka, Prague, Czech Republic

**Materials and methods:** We show three patients with extreme large secondary chondrosarcomas that were presented late with already spread disease. Radiological evaluation of these patients is presented together with the results of controversial treatment that surprisingly showed benefit.

**Results:** First patient was a bed ridden male with huge chondrosarcomas of the pelvic as well as shoulder girdle. Interthoracoscaphular amputation and hemipelvectomy on the ipsilateral side were carried out. After the surgery he started to ambulate in a wheelchair and was able to move around at home. He died two years after surgery on lung metastases with an only minimally symptomatic pelvic local recurrence.

Second patient is a female with multiple enchondromatoses presented with a large chondrosarcomas on the anterior part of the proximal femur growing from the lesser trochanter anteriorly. A wide resection was planed with a tumor endoprosthesis. Nevertheless further enchondromas showed radiological signs of malignisations. Due to this only an marginal resection of the extraosseal part with resection of the lesser trochanter were performed and the hip was preserved. She achieved immediate full range of motion in the hip and had a quick recovery into normal life.

The third patient is a female with a history of over 30 years growing mass from the chest wall starting below the diaphragm on the right side pushing the liver high up into the chest wall. It started to grow also caudally into the pelvis. Surprisingly the women refused to go to see a doctor with the growing mass, but first visited the orthopedic specialist because she could not sit properly due to a limited flexion in the hip from the growing pelvic mass. The tumor exulcerated in the dorsal thoracic part and general as well as chest surgeons so far refused surgical intervention.

**Conclusion:** Secondary chondrosarcoma is an, at first only slowly growing tumor that some patients accept as part of their normal life and refuse treatment until other problems occur. In such large tumors that are at least potentially multifocal, it is always difficult to choose between overtreatment and undertreatment. The patient has to be evaluated individually and sometimes we can see a surprisingly great improvement in life quality even after a mutilating surgical procedure even if only for a limited period of time. In such cases an intralesional procedure can be justified taking into advantage the fact, that chondrosarcomas are hypovascular tumors and that repeated extirpations can be performed for the residual or relapsed tumor.

# EVOLUTION OF EXTRA ABDOMINAL AGGRESSIVE FIBROMATOSIS : ANALYSIS BASED ON A “WAIT AND SEE” POLICY.

005

F. Gouin, P. Anract, O. Barbier, G. Odri, E. Bompas, S. Briand

University Hospital of Nantes, France

Bone tumor Research Laboratory, UMR 957 Inserm, University of Nantes, France

University Hospital of Cochin-Port Royal, Paris, France

West Institut of Cancer, Nantes-Angers, France

**Introduction:** Extra-abdominal aggressive fibromatosis (EAAF) are benign soft tissue tumors with a potential of local aggressive behaviour due to a clonal fibroblastic proliferation. The mainstay of treatment has been wide surgical resection for decades, leading to high rate of local recurrence and frequent severe functional impairment. For these reasons, and the unpredictable outcome of this disease, the benefit of surgery is currently questionable. Thus, “wait and see” (W&S) policy (no aggressive surgical or irradiation treatment) can lead to stabilization of the disease in a subset of patients. The aim of this study is to describe course of native or recurrent EAAF based on the retrospective study of 48 patients.

**Patients and methods:** Forty eight patients (2 bone and soft tissue tumor referent centers) with histologically proved EAAF were involved in the study. The W&S policy was proposed after a multidisciplinary decision that relied on arbitrary criterias at the diagnosis (patient and tumor status, site, size) and was the first line approach for all patients during the past 5 years. All patients were followed up every 6 months during the tumor progression period (clinical and MRI assessments) and then every year. The stability of the tumor was decided when no progression was seen between two successive MRI.

**Results:** Twenty five patients were treated with this conservative approach after biopsy and 13 after 1 or several local recurrences. Medical a treatment was proposed for symptomatic patients, including painkillers and nonsteroid anti-inflammatory drugs. Tamoxifen has been proposed in some growing tumors and chemotherapy in one case.

In 47 of the 48 patients, the tumors stopped their progression (with 5 cases of total regression 10%). The median duration of progression was 9 months for native tumors and 14 months for recurrent tumors. The mean follow-up after stabilisation was 71 months (2- 258). Only one tumor had had a progression period of more than 36 months (49 months). For two patients, after growth arrest, a second step of progression was observed during one year, and they are now stable since more than 2 years for each.

Only one patient had a worrying progression of a chest wall tumor, despite chemotherapy and radiotherapy : she was operated after 3 years of progression, with no recurrence at 5 years of follow-up.

Pain and function impairment were in all cases stable or improved.

**Conclusion:** This study confirms that W&S conservative approach for native or recurrent EAAD can lead to long lasting stabilization of the tumor. In our hands, the first 3 years after diagnostic is the most critical period as no tumor except one had progressed after 36 months. Symptomatic treatment and psychological approach are necessary for the patient during this period, especially when the tumor is close to neurovascular bundles. Despite this approach is our nowadays first line treatment, the methodology of this study is unable to identify prognostic factors to choose which patient is eligible for this conservative approach and literature is very poor on that topic.

Zdzislaw Krol<sup>1</sup>, Pawel Skadlubowicz<sup>2</sup>, Fritz Hefti<sup>1</sup>, Andreas H. Krieg<sup>1</sup>

<sup>1</sup>Paediatric Orthopaedic Department, Children's University Hospital Basel (UKBB) Spitalstrasse 33, 4056 Basel, Switzerland

<sup>2</sup>Department of Biomedical Computer Systems, Institute of Computer Science, Faculty of Computer Science and Materials Science, University of Silesia, 41-205 Sosnowiec, Poland

**Background:** Bone tumor in the pelvis region usually causes its deformation and destruction. Preservation of the biomechanical characteristics of the pelvis after a large periacetabular resection due to a malignant pelvic tumor is challenging. The reconstruction of the resected osseous structures around the acetabulum using allogeneous transplants or artificial implants is not satisfying and the orthopedic surgeons try to design and apply ever more often patient-specific implants. Because the original anatomy of the pelvis cannot be adequately assessed at the tumor site, methods for its reconstruction are required. The widely used strategy for planning the reconstruction of the resected part of the pelvis is the mirroring of the contralateral side. We propose a novel planning method for reconstruction of pelvis defects.

**Method:** Our approach utilizes pelvic statistical shape models to generate patient-specific implant geometries. This parametric pelvic model can be manipulated to optimally match a patient's pelvic anatomy. The main objectives of this study were to present and evaluate the virtual anatomical reconstruction of eight tumor-damaged pelvic bones using the pelvic statistical shape model. This included also a comparison with the mirroring method. The collected and segmented CT datasets were subdivided into male ( $n=50$ ) and female ( $n=50$ ) pelvises, and a gender-specific statistical shape model was generated from each dataset collection.

**Results:** We achieved an overall mean deviation distance of 0.89 mm (for the intact area) and 1.26 mm for the reconstruction of the equivalent defect in the healthy hemipelvis (for the whole hemipelvis area). The comparison with the mirroring of the contralateral side approach shows the same reconstruction quality level.

**Conclusion:** In the clinical case application both virtual reconstruction approaches the mirroring and the SSM-based one reconstruct the defect at the same clinically acceptable accuracy level. Clinically speaking, a surface deviation error in the range of 1 mm is a very good result. This study demonstrates that the presented model can be a valuable tool for the planning of pelvic reconstructive surgery and implant design.



## SORAFENIB AND DACARBAZINE IN SOFT TISSUE SARCOMA: A SINGLE INSTITUTION EXPERIENCE

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Vincenzi B<sup>1</sup>, Silletta M<sup>1</sup>, Schiavon G<sup>2</sup>, Frezza AM<sup>1</sup>, Del Vescovo R<sup>1</sup>, Dei Tos AP<sup>3</sup>, Zobel BB<sup>1</sup>, Santini D<sup>1</sup>, Tonini G<sup>1</sup>.

<sup>1</sup>University Campus Bio Medico, Rome, Italy

<sup>2</sup> Department of Medical Oncology, Erasmus University Medical Center - Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

<sup>3</sup>Azienda ULSS 9 Treviso, Treviso, Italy

**Background:** To report on the antitumor activity and toxicity of sorafenib combined with dacarbazine in patients with pre-treated advanced soft tissue sarcoma (STS).

**Method:** Our phase II study enrolled 17 consecutive patients (..men/..women) affected by STS with a performance status  $\leq 2$  and measurable disease, who failed two or more previous regimen of chemotherapy, from November 2009 to December 2010. All the patients received continuous dosing of sorafenib 400 mg twice daily and dacarbazine 300 mg/m<sup>2</sup> for 3 consecutive days every 21 days until disease progression (PD) or intolerable toxicity.

**Results:** A total of 14 patients were evaluable for response, having 3 patients stopped treatment early due to death for non-disease related reasons and rapid clinical deterioration (1 and 2 patients, respectively). No complete responses were observed. As by RECIST, partial responses (PR) were recorded in 3 patients (21%), stable disease (SD) in 6 patients (43%), and PD in 5 patients (36%), with a clinical benefit (PR+SD>6 mos) of 64%. The median progression-free survival was 20 weeks (range: 9-34) and the median overall survival was 43.5 weeks (range: 17-65). The main recorded toxicities were: neutropenia (36%), thrombocytopenia (36%), hypertension (36%), fatigue (50%), and skin reactions (57%). Five patients required dose reductions (both drugs) for toxicity and 3 patients required only sorafenib reduction due to skin reactions. One patient went off-study because of severe sorafenib-related dermatologic toxicity.

**Conclusions:** Sorafenib and dacarbazine combination seems to be an active and safe regimen in pre-treated STSs. A phase II study is currently ongoing in patients affected by selected sarcoma subtypes.

Kruseova J.(1), Krizkova L.(2), Bunesova M.(3), Hynek D.(2), Adam V.(2), Kizek R.(2), Eckschlager T.(1)

1. Department of Paediatric Haematology and Oncology, Motol Hospital, Prague.

2. Department of Chemistry and Biochemistry, Faculty of agronomy, Mendel University, Brno.

3. Department of Clinical biochemistry and Pathobiochemistry, Motol Hospital, Prague.

**Introduction:** Metallothioneins (MTs) are low molecular (cca 6kDa) cystein rich proteins, which have naturally occurring  $Zn^{2+}$  in both binding sites. MTs participate in the carcinogenic process, but their use as a tumor marker or predictive marker remains controversial. MTs are necessary for metal transport and protection against metal and ROS toxicity, what can influence chemotherapy effectiveness.

**Objectives:** to understand relationship between MTs serum levels and different treatment and posttreatment period with correlation to tumor activity and chemotherapy side effects.

**Materials and methods:** prospective observational study involving a sample of 194 patients with child solid tumors treated from 2008 – 2011. Median age of patients was 10,09 years. Examined were 756 serum samples. MTs were determined in blood serum using differential pulse voltammetry - Brdicka reaction.

**Results:** The average level of MTs was 3,4  $\mu\text{mol/l}$ . There was correlation between MTs level and increased creatinine  $p < 0,002$  in all solid tumor. Different level of MTs between complete remission and active disease was found only in osteosarcoma  $p < 0,016$  and germ cell tumors  $p < 0,007$ . The last two diagnosis had highest amount of patients with increased creatinine level caused by platinum based chemotherapy.

**Conclusions:** we found new correlation between kidney function and MTs level. Our results support hypothesis that MTs involve chemotherapy effectiveness.

**5 key references:** serum metallothionein levels, differential pulse voltammetry, solid tumors, kidney function, chemotherapy

# PRELIMINARY DATA OF HIF-1A EXPRESSION IN 50 CHORDOMA SPECIMENS: A POTENTIAL ADJUVANT THERAPEUTIC TARGET?

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E.V. Froehlich<sup>1</sup>, S. Scheipl<sup>1</sup>, C. Wibmer<sup>1</sup>, P. P. Varga<sup>2</sup>, A. Lazáry<sup>2</sup>, F. Quehenberger<sup>3</sup>, B. Liegl<sup>4</sup>, A. Leithner<sup>1</sup>.

<sup>1</sup> Department of Orthopaedics and Orthopaedic Surgery, Medical University Graz, Austria

<sup>2</sup> National Centre for Spinal Disorders, Budapest, Hungary

<sup>3</sup> Institute of Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria

<sup>4</sup> Institute of Pathology, Medical University of Graz, Austria

**Objectives:** Chordomas are known as intermediate-grade malignant tumors that show a slow but destructive growth. To date standard treatment consists of surgery and radiotherapy, often ending in recurrent disease. An explanation for the high recurrence rates might be the involvement of HIF-1 $\alpha$  (Hypoxia-inducible factor) in the tumor progression, such as angiogenesis, metabolism, cellular growth, metastasis, and apoptosis. Therefore, the aim of the present study was to investigate the expression of HIF-1 $\alpha$  in chordomas by immunohistochemistry.

**Materials and Methods:** The study-group included 50 Brachyury-verified chordoma specimens (34 primary, 16 recurrent tumours), obtained from 27 males and 17 females. At time of diagnosis the patients' age ranged from 24 to 90 (mean 53.9 ys.). Tumours were located in the skull, the sacrum/coccyx and the spinal column in 11, 20, and 13 cases, respectively. Tumour-volume ranged from 0.6 to 2720cm<sup>3</sup> (mean 324.6cm<sup>3</sup>). Follow-up, available in 39 cases, ranged from 2 to 234 months (mean 68 months). Immunohistochemistry was performed with monoclonal antibodies against HIF-1 $\alpha$ . Staining-pattern and positive tumour-cells were evaluated.

**Results:** HIF-1 $\alpha$  expression was obtained in 26/34 (76.5%) of the primary chordomas and in 15/16 (93.7%) of the recurrent cases. The staining-pattern was cytoplasmic in 19 and cytoplasmic/nuclear in 22 cases. Nine cases were negative. Of the primary lesions 5 showed 1+ staining (0-49% of chordoma cells reactive), 21 cases 2+ staining (50-100% of chordoma cells reactive). Recurrent chordomas showed a 1+ staining in 4 cases and 2+ staining in 11 tumors, respectively.

**Conclusion:** Enbloc resection with tumor-free margins is seldom feasible, particularly in the sacrum. Intralesional excisions mostly end in early local recurrence; therefore, the demand for further treatment options is frequently posed. Recently published studies on solid malignancies have shown that an enhanced sensitivity towards radio- but also chemotherapy can be achieved by the selective suppression of HIF-1 $\alpha$ . Thus our results may indicate that a specific HIF-1 $\alpha$  targeting in chordomas could be a future adjuvant therapy strategy to increase the respond to radio- and especially chemotherapy in these tumors.

# TUMOUR GRAFTS DERIVED FROM SARCOMA PATIENTS MIMIC TUMOUR PATHOLOGY, VIABILITY AND INVASION IN THE CHICK CHORIOALLANTOIC MEMBRANE MODEL

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Gwen Sys<sup>°</sup>, Ramses Forsyth<sup>°°</sup>, Ian Peeters, Mieke Van Bockstal<sup>°°</sup>, Maurice Balke<sup>\*\*</sup>, Bart Poffyn<sup>°</sup>, Dirk Uyttendaele<sup>°</sup>, Marc Bracke<sup>\*</sup>, Olivier De Wever<sup>\*</sup>.

Gwen Sys, MD

<sup>°</sup>Department of Orthopaedic Surgery and Traumatology  
Ghent University Hospital  
De Pintelaan 185 - B – 9000 Ghent, Belgium

<sup>\*</sup>Department of Radiation Oncology and Experimental Cancer Research  
Ghent University

<sup>°°</sup>M. Ghormaghtigh Institute of Pathology  
Ghent University Hospital

<sup>\*\*</sup> Department of Trauma and Orthopaedic Surgery  
Witten/Herdecke University, Faculty of Health - School of Medicine  
Cologne Merheim Medical Center - D-51109 Cologne, Germany

Sarcomas, or tumours of the musculoskeletal system, are very rare. In this study, fresh tumour samples were used to establish whether the chick chorioallantoic membrane (CAM) assay can be used to evaluate the viability of these tumours and to examine their migrational, invasive and angiogenetic behaviour.

Material and methods: Fresh tumour material was obtained from 28 consecutive patients with an aggressive benign or malignant bone or soft-tissue tumour. Digital images were used to score angiogenesis according to the Ausprunk classification. Histological evaluation and scoring of graft (viability, necrosis, infiltration) and host (vascular ingrowth, bleeding and CAM hyperplasia) behaviour was performed by three observers according to protocol.

Results: Correct histological diagnosis remained possible after harvesting of the CAM. Less than half of the tumour samples proved to be viable, with marked differences between patients. Chemotherapy had an adverse effect on tumour invasiveness. Metastatic lesions proved to be very viable and showed marked vascular ingrowth. Infiltration of fibroblasts from the CAM into the tumour samples is thought to herald vascular ingrowth. Macroscopic vascular reaction did not correlate with microscopic vascular ingrowth.

Conclusion: The CAM assay can be used to study fresh material derived from tumours of the musculoskeletal system and proved to be a useful tool for the evaluation of tumour sample viability and its locally invasive behaviour. We suggest using the xenograft CAM assay to generate a sarcoma study population that could be profiled for biomarker assessment and randomized for prospective treatment with targeted agents.

**Key words:** CAM assay, sarcoma, targeted agents, xenograft model, angiogenesis

## THE USE OF TOTAL CT IN DETECTING DISTANT METASTASES OF BONE SARCOMAS.

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Kobys V.L.<sup>1</sup>, Ternitskaya Y.P.<sup>4</sup>, Konovalenko V.F.<sup>2</sup>, Klusov A.N.<sup>1</sup>, Repina N.V.<sup>3</sup>, Matyushok O.F.<sup>1</sup>

<sup>1</sup> Kyiv City Oncology Hospital. <sup>2</sup> "Fresenius" Representation in Ukraine. <sup>3</sup> Oberig Clinic, Kiev. <sup>4</sup> Center of Radiodiagnostics, Academy of Sciences of Ukraine

**Introduction:** According to the ESMO 2009 recommendations for examination of patients with bone sarcomas, it is necessary to study the primary lesion, two adjacent joints, the chest, and perform bone scan. Our observation indicates this amount of research for the staging of the disease to be inadequate.

**Materials and Methods:** In the children's department in the period from May 2010 to February 2012 for staging the disease, a total spiral computed tomography was performed in addition to the standard study. We examined 16 children aged 8 to 18, 5 with Ewing's sarcoma and 9 with osteogenic sarcoma. The study was conducted on a 64-slice General Electric computer tomograph, Light Speed VCT model, 1.25 mm slice thickness, 2.5 mm pitch, with further slice reconstruction 0.625 mm. Contrast enhancement was not performed.

**Results:** In 2 of 16 patients (12.5% of patients) individual lesions were revealed that were not detected by bone scan. They were located in the medullary canal of the humerus in a patient with a lesion of the radius of the same limb and in the medullary canal of the diaphysis of the femur of the opposite limb.

**Conclusions:** Total computed tomography using modern devices in patients with bone sarcomas may be an alternative to total magnetic resonance imaging in the examination of patients.

Kobys V.L.<sup>1</sup>, Konovalenko V.F.<sup>2</sup>, Klusov A.N.<sup>1</sup>, Repina N.V.<sup>3</sup>, Dolinsky F.S.<sup>1</sup>, Zaharycheva E.V.<sup>4</sup>, Matyushok O.F.<sup>1</sup>

<sup>1</sup> Kyiv City Oncology Hospital. <sup>2</sup> "Fresenius" Representation in Ukraine. <sup>3</sup> Oberig Clinic, Kiev. <sup>4</sup> Kyiv City Children's Hospital No. 7.

**Introduction:** Late infection of oncoendoprosthesis is a threatening complication that can ultimately lead to amputation. Existing approaches in the treatment of this pathology (removal of the festering endoprosthesis, installation of a temporary cement spacer impregnated with antibiotics, long-term antibiotic therapy, repeated reconstructive surgery) cannot ensure recovery of all patients.

**Materials and Methods:** In a group of three patients aged 19-22 years who received knee endoprosthesis in 2004, 2005, 2006 due to distal femur osteosarcoma, endoprosthesis infection occurred 3-4 years after surgery. The reasons were: tooth infection, lengthening of the implant, unknown reason. *Staphylococcus aureus* was plated in 2 patients, *Staphylococcus epidermidis* in 1 patient. Treatment consisted of removal of the endoprosthesis, installations of the spacer (from 2 to 5 times in one patient), prolonged antibiotic therapy for about two years. The extremities were not bent at the knee joint. After 3-4 months, spacer re-infection was observed. It was decided to perform complete removal of the spacer in all patients, install a rod apparatus for external fixation of bone fragments. After 4-5 months, reimplantation of endoprosthesis impregnated with silver was performed.

**Results:** In all patients an excellent functional result was received: the flexion function of the knee is fully recovered; there is no evidence of infection from 9 months to 1 year after surgery. One patient is pregnant, another one returned to her job, and the third one is preparing for enrollment at a university.

**Conclusions:** Treatment of infections of oncologic prostheses should be more aggressive with the removal of foreign bodies in contrast to the treatment of infections of orthopedic endoprotheses. .

# LONG TERM RESULTS OF MINIMALLY INVASIVE ENDOPROSTHETIC REPLACEMENTS IN CHILDREN

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V Neelapala, R Grimer, S Carter, R Tillman, A Abudu, L Jeys  
Royal Orthopaedic Hospital, Birmingham

**Aim:** To assess the outcomes in terms of prosthetic survival and complications of children who underwent a minimally invasive Stanmore growing prosthesis.

**Method:** Retrospective review of all patients treated identifying complications and outcomes.

**Results:** 140 children between the ages of 2 and 16 had a minimally invasive prosthesis inserted between 1992 and 2011. All were for bone tumours, 99 being osteosarcoma and 35 Ewing's sarcoma. There were 59 distal femur, 25 proximal humerus, 34 proximal tibia, 15 proximal femur, 3 midshaft femur, 2 total femur, 2 total humerus prostheses.

48 patients have died, 2 after renal failure the rest from metastases. Survival is 69% at ten years. There were 18 local recurrences, 9 of these patients have died.

12 patients had an amputation of which 8 were for local recurrence and 4 infection. 74 of the patients had one or more lengthening (average 3.6). 15 patients had a problem with lengthening (either shortening, spontaneous lengthening or failure) and five needed revision for problems with this. There were three infections after a lengthening (1.1% risk). 37 of the implants needed revision of which 30 were done as single stage procedure and 5 were done as two stage revision for infection. Survival of the implant without revision or amputation was 52% at 5 years and 42% at ten years but all patients had undergone a revision by 15 years. There was no obvious difference in survival of the implants when split by site, age at time of insertion or diagnosis. Most surviving children had a limb length discrepancy of less than 2cm.

**Conclusion:** The minimally invasive extendable prosthesis has proved effective and safer than anticipated. The rate of infection despite repeated lengthenings is under 4% but revision appears to be inevitable within 15 years.



# HAS ASEPTIC LOOSENING IN DISTAL FEMORAL ENDOPROSTHETIC REPLACEMENT BEEN ABOLISHED BY THE INTRODUCTION OF THE HYDROXYAPATITE COLLAR?

072

JRW Glanville, AE Simpson, RJ Grimer

Royal Orthopaedic Hospital NHS Foundation Trust, Orthopaedic Oncology Department, Bristol Road South, Northfield, Birmingham, B31 2AP, UK.

**Aim:** Aseptic loosening has been one of the main causes of failure of joint replacements. This is a particular problem following bone tumour resections and reconstruction with endoprosthetic replacement (EPR), as the patients are often young and active. The introduction of a hydroxyapatite (HA) collar seemed to have significantly decreased this problem at medium term follow up. We have reviewed the 19 year experience of prosthesis failure in patients with a distal femur EPR incorporating the HA collar.

**Method:** Survival information was collected from a prospective database for all patients who underwent a custom made distal femoral EPR with an HA collar between September 1991 and December 2011. Outcomes were recorded in terms of patient death (implant *in situ*), survival of implant, failure of implant, or amputation and were split by whether the procedure was primary or secondary.

**Results:** Over the past 19 years, 362 distal femoral EPRs with an HA collar have been inserted, 261 as primary cases and 101 as secondary procedures. 54 patients required further revision due to: infection (n=24), aseptic loosening (n=10), implant fracture/failure (n=17) or metal allergy (n=3). There were 20 amputations (local recurrence n=13; infection n=7). Using Kaplan-Meier survivorship analysis, at 19 years there was a 7% chance of aseptic loosening and 11% risk of infection. The risk of further major surgery (amputation or revision for any cause) was 37.7% at 19 years. There was no significant difference in the incidence of aseptic loosening or infection between primary and revision prostheses, even when the revision was done for a previous failed EPR.

**Conclusions:** Aseptic loosening has been markedly reduced since the introduction of the HA collar with rotating hinge. There is no greater risk of implant failure in terms of aseptic loosening in patients requiring revision surgery as opposed to primary.

## PROLIFERATION OF OSTEOSARCOMA CELLS TARGETED BY SMALL MOLECULES IN A HIGH-THROUGHPUT APPROACH

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Doris M. Seiler<sup>1,2</sup>, Jan Smida<sup>1,2</sup>, Stephanie Zillmer<sup>1,3</sup>, Ina Rothenaigner<sup>4</sup>, Kenji Schorpp<sup>4</sup>, Kamyar Hadian<sup>4</sup>, Daniel Baumhoer<sup>1,5</sup>, and Michaela Nathrath<sup>1,2</sup>

<sup>1</sup> Clinical Cooperation Group Osteosarcoma, Helmholtz Zentrum München – National Research Centre for Environment and Health, Neuherberg, Germany

<sup>2</sup> Department of Pediatrics, Technische Universität München and Pediatric Oncology Center, Munich, Germany

<sup>3</sup> Department of Pediatric Oncology, Klinikum Kassel, Kassel, Germany

<sup>4</sup> Institute of Toxicology, Helmholtz Zentrum München – National Research Centre for Environment and Health, Neuherberg, Germany

<sup>5</sup> Bone Tumor Reference Center at the Institute of Pathology, University Hospital Basel, Basel, Switzerland

Tumor malignancy is correlated to tumor progression and invasiveness into surrounding tissues. Comparative analysis of various osteosarcoma (OS) cell lines showed different behavior of OS cells in proliferation, invasiveness and migration *in vitro*. These phenotypes were associated with differential expression of specific miRNA, indicating that miRNA deregulation influences cell migration and proliferation.

Here we present a strategy for screening in a high-throughput manner of biological active compounds that might affect the proliferative behavior of OS cells. We established an automated pipetting system and subsequent quantitative measure of cell proliferation and apoptosis for screening of the effect of a large set of small, non-toxic compounds (>10.000) on our set of OS cell lines. First experiments show that cell viability and apoptosis can be robustly determined using the high-throughput approach. We currently investigate the effect of specific miRNA inhibition and mimic, respectively, on cell proliferation in comparison to treatment with small molecule inhibitors and other known proliferation inhibitors.

The compounds are often used for inhibition of target molecules and for identification of specific pathways that are represented by a specific cell phenotype. Thus, we plan to mimic miRNA effects on cell proliferation using these compounds and to finally identify targets and pathways involved in osteosarcoma progression. Taken together, regulative mechanisms, such as miRNA regulation might be targeted by small molecules to influence the metastatic potential of osteosarcoma cells and improve prognostic and individual therapeutic strategies.

Elisa Tavanti, Valeria Sero, Serena Vella, Francesca Michelacci, Marilù Fanelli, Claudia Hattinger, Maria Cristina Manara, Lorena Landuzzi, Piero Picci, Massimo Serra

Laboratory of Experimental Oncology, Orthopaedic Rizzoli Institute, Bologna, Italy

**Objectives:** In order to improve the survival rate of osteosarcoma patients, it is necessary developing novel therapies. Although osteosarcoma has not been studied as well as other types of cancer, different kinases have been indicated to be involved in its pathogenesis and progression. Deepening the role of specific protein kinases in osteosarcoma may therefore indicate new candidate therapeutic markers, which can be targeted by specific inhibitor drugs that have emerged as attractive compounds for development of targeted treatments in other human tumours.

Objective of this study was the preclinical validation of protein kinases and kinase inhibitors of possible clinical usefulness in osteosarcoma.

**Materials and Methods:** By mining genome-wide expression profiling data obtained from 21 osteosarcoma clinical samples, the following five protein kinases emerged as the most relevant for the osteosarcoma biology: AURKA, AURKB, CDK2, PIK3CA, PLK-1. These five kinases received the highest priority from the *in silico* analyses on the basis of their expression pattern and because they are: 1) drugable, 2) frequently over-expressed in osteosarcoma at clinical onset, 3) associated with highly malignant features, and 4) expressed at higher levels in osteosarcomas compared to normal musculoskeletal tissues. Analysis of the osteosarcoma cell dependency from these kinases by RNA interference (RNAi) revealed that Aurora kinase A (AURKA) and Aurora kinase B (AURKB) were the most relevant for osteosarcoma cell lines growth and survival. We therefore investigated the efficacy of the two Aurora kinases inhibitors VX-680 and ZM-447439, which have already been included in clinical trials for other tumors. Chemosensitivity against VX-680 and ZM-447439 was investigated on four drug-sensitive and six drug-resistant human osteosarcoma cell lines and the *in vitro* efficacy of each drug was estimated in terms of cell growth inhibition, cell cycle perturbations and apoptosis induction. The impact of each drug on the malignant phenotype of osteosarcoma cells was assessed by evaluating its effects on the *in vitro* cell motility and on the cloning efficiency in nonadherent conditions (soft-agar). Finally, VX-680 and ZM-447439 activity was analysed in combination with conventional chemotherapeutic agents (doxorubicin, methotrexate or cisplatin).

**Results:** The sensitivity to VX-680 and ZM-447439 was quantified by evaluating the IC50 value of each cell line (Tables 1-2).

In terms of cell growth inhibition, all cell lines proved to be more sensitive to VX680 than to ZM447439. Cell growth inhibition was caused by a remarkable phase S accumulation more than an apoptosis induction, suggesting that these drugs have cytostatic rather than cytotoxic effects on osteosarcoma cell lines. A decrease of drug sensitivity was observed in doxorubicin-resistant cell lines (which are characterized by a high expression of ABCB1), indicating that VX680 and ZM-447439 are most probably ABCB1 substrates. VX680 also decreased motility and soft-agar colony formation ability of human osteosarcoma cells.

Drug association experiments showed that VX680 positively interacts with all conventional chemotherapeutics, indicating that it can be used in combination with the drugs included in osteosarcoma treatment protocols. Of particular relevance was the observation of a synergistic interaction between VX680 and cisplatin (CDDP) in CDDP-resistant cell lines, a result that supports the Aurora kinases involvement in CDDP resistance, as described for other tumours.

**Conclusions:** These results indicate that Aurora kinases might represent new candidate therapeutic targets for osteosarcoma, being frequently highly expressed and playing an important role in osteosarcoma cell growth. *In vitro* analysis of two Aurora kinase inhibitors *in vitro* activity indicated in VX680 a new promising candidate drug of potential clinical usefulness to target these molecules.

Table 1.

VX-680	Mean $\mu$ M	s.d.
U-2OS	0,376	0,16
Saos-2	0,365	0,168
IOR/OS18	2,210	0,480
IOR/OS9	0,220	0,149
U-2OS/MTX300	0,58	0,03
Saos-2/MTX300	0,28	0,17
U-2OS/DX580	52,77	6,44
Saos-2/DX580	16,3	2,53
U-2OS/CDDP4 $\mu$ g	15,16	1,24
Saos-2/CDDP6 $\mu$ g	8,4	2,59

Table 2.

ZM-447439	Mean $\mu$ M	s.d.
U-2OS	2,67	0,12
Saos-2	2,63	0,29
IOR/OS18	5,5	1,2
IOR/OS9	0,67	0,17
U-2OS/MTX300	4,3	0,38
Saos-2/MTX300	0,6	0,17
U-2OS/DX580	11,23	2,28
Saos-2/DX580	13,82	2,33
U-2OS/CDDP4 $\mu$ g	4,43	1,04
Saos-2/CDDP6 $\mu$ g	2,75	0,82

## PALLIATIVE TREATMENT OF SOFT TISSUE SARCOMA WITH TRABECTEDIN

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Joana Godinho<sup>1</sup>; Filipa Carneiro<sup>1</sup>; Rosa Vallinoto<sup>1</sup>; Ana Ferreira<sup>1</sup>; José Dinis<sup>1</sup>; Marta Soares<sup>1</sup>; Mariana Afonso<sup>2</sup>; Jorge Guimarães<sup>3</sup>.

1 – Department of Medical Oncology; 2 – Department of Pathology; 3 – Head of the Sarcoma Unit.

Portuguese Institute of Oncology, Oporto, Portugal.

**Background:** Soft tissue sarcomas (STS) are a rare and heterogeneous group of tumours that derive from mesenchymal cells and include a variety of histological subtypes. Despite treatment of the primary tumour, 50% of patients ultimately develop metastases or local recurrence. Metastatic disease treatment frequently depends on chemotherapy and median survival ranges from 6 to 12 months. Standard chemotherapy regimens usually include Doxorubicin and Ifosfamide either in combination or monotherapy. Trabectedin has shown to improve response rate and overall survival in STS that has progressed after the use of those agents and whenever they are contra-indicated.

**Objectives:** Our purpose was to assess the effectiveness of Trabectedin in a cohort of metastatic STS patients.

**Material and Methods:** Retrospective cohort study, in a Portuguese cancer centre, of all STS patients treated with Trabectedin. Comorbidity was assessed by Charlson's index. Toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 3. Efficacy was evaluated by time to progression and overall survival using Kaplan-Meier's method. A 95% confidence interval was used.

**Results:** From July 2009 till February 2012, 13 STS patients were treated with Trabectedin. Median age was 55 (range 24-79; 15,4% > 65 years), 69,2% were female, all had ECOG performance status  $\leq 1$  and 61,5% had a Charlson's comorbidity index of 0. The most common histological subtypes were Leiomyosarcoma (38,5%), Liposarcoma (23,1%) and Synovial sarcoma (15,4%). Over 80% of patients had previously been submitted to chemotherapy with Doxorubicin and Ifosfamide. Six or more cycles were accomplished by 46% of patients and a relative dose-intensity  $\geq 80\%$  was achieved in 54% of pts. Grade 3 or 4 adverse events occurred in 61,5% of patients and the most common were neutropenia (30,8%) and infection (23,1%). Two patients died due to treatment toxicity. Stable disease was achieved in 50% of patients and 20% had partial response. Median duration of response was 5 months [95CI, 2,4 – 7,6]. Median time to progression was 9 months [95 CI, 3,5 – 14,5] and 61% of patients were alive at 24 months of follow-up after the start of Trabectedin.

**Conclusions:** Our results strengthen the benefit of Trabectedin's use in the treatment of metastatic soft tissue sarcomas. Its toxicity profile presents a challenge to the selection and management of patients during treatment. The small sample size is a limitation of this study.

Leithner A, Pirker-Fruehauf U, Friesenbichler J, Wibmer C

Department of Orthopaedic Surgery, Medical University of Graz – Graz - Austria

**Objectives** Female gender has been reported as an independent factor for survival in osteosarcoma patients. Furthermore male gender seems to be at higher risk for osteosarcoma development. The aim of the study was to accumulate recent and sex-specific data on incidence and mortality of osteosarcoma patients.

**Materials and Methods:** We used the cumulative osteosarcoma incidence rate from the CDC Wonder database for 1999-2008, which provides incidence data for nearly the whole U.S. population, including 8803 patients with osteosarcoma. Sex-specific data were obtained for six 5-year age groups between 1 and 39 years including 5970 patients. For mortality data a PubMed search was conducted for comparison of major treatment studies published after 2000.

**Results:** For the age group between 1 and 40 years the annual incidence for female osteosarcoma patients was 3,4 per 1.000.000, while the incidence for male patients was 4,3 per 1.000.000 (1:1,33;  $p < 0,001$ ). Mortality data favored female gender in nearly all studies although differences exist if sex can be regarded as an independent factor.

**Conclusions:** While the causes for the higher incidence for male osteosarcoma patients remain totally unclear, there are at least some possible explanations for worse male survival. The presented statistical data from the U.S. confirm the previously reported later peak in the male group (female 10-14 yrs; male 15-19 yrs) and therefore a possible decreased susceptibility to chemotherapy. If an additional gender-specific approach to chemotherapy should be applied still remains elusive.

# TREATMENT OF PRIMARY ANEURYSMAL BONE CYST (ABC) WITH CURETTAGE AND THREE CROSSED KIRSCHNER WIRES (K/W). PRESENTATION OF TWO (2) CASES.

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*Konstantinos Tsanidis*

*Consultant Orthopaedic Surgeon – Sarcoma Surgeon*

*Orthopaedic Dept.*

*“Saint Luke” Private Hospital,*

*Panorama, Thessaloniki, GREECE.*

Primary aneurysmal bone cyst is a benign cystic lesion of bone. It is an extensile cystic lesion and can cause extensive weakening of the bony structure and impinge on the surrounding tissues. It is composed of blood filled spaces separated by connective tissue septa containing fibroblasts, osteoclast type giant cells and reactive woven bone. Etiology and pathophysiology remain uncertain. Often affects individuals during their second decade of life and may occur in any bone in the body. The treatment of choice is intralesional curettage with significant rate of recurrence. Other surgical options include en bloc resection or wide excision, selective arterial embolization, and curettage with locally applied adjuvants such as liquid nitrogen or phenol.

It presented a method of treatment consisted in curettage and the use of three (3) crossed K/W. Two boys patients (A & B), 4 and 14 y.o., respectively, were treated with this method on 2009 and on 2010. In both patients the symptoms were pain, swelling and discomfort of the adjacent joint. To the patient A the affected site was the right distal radius, very close to the growth plate and to the patient B the 2<sup>nd</sup> right metatarsal bone. The imaging, x-ray and MRI, revealed a cystic, extensile lesion with increased weakening of the cortex. The CT guided needle biopsy confirmed in both the diagnosis of the primary ABC. The choice of intralesional curettage and the use of 3 K/W was adopted because the parents were not so enthusiastic with the idea of taken auto grafts from the iliac bone or with the use of synthetic grafts. The first patient (A) operated with this method on 2009 and the second (B) on 2010. The follow-up showed healing of the ABC without any recurrence and with progressive restoration of the affected bone.

The K/W were removed after the completion of a year after surgery. The latest

x-rays control revealed remarkable healing without any trace of the pre-existing lesion. The role of the 3 K/W remains obscure but in the past were used less and more K/W without success and with formation of abnormal or hypertrophic bone.

The K/W plays a role of scaffold and there is a correlation to the pressure – electric phenomenon and to the Wolf's law for the orientation of the bony lacunae but the answer why only the 3 K/W offers the ideal result in bone reorientation remain uncertain and under study.

The two patients, today, clinically and imaginarily present no evidence of disease or recurrence.

Kharatishvili TK, Martynkov DV, Buydenok YV, Narkevich BJ, Fedenko AA, Petrachenko NS, Dolgushin BI, Aliev MD

FGBU N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences

Moscow, Russian Federation

**Objective:** To estimate the effectiveness of using the technique of isolated limb perfusion in the RCRC RAMS

**Materials and methods:** In the treatment of locally advanced forms of melanoma and soft tissue sarcomas using new methods of local treatment. Isolated regional chemotherapeutic perfusion, according to international studies, is an effective method in the affected limb. In Russian Cancer Research Center in 2010-2012 were treated 13 patients (13 ILP's). Female - 10 (77%), male - 3 (23%), mean age  $51 \pm 17,5$  years, range 21-79 years. Patients underwent ILP via the femoral (n = 12) and axillary (n = 1) approach. The distribution by histological type of tumor: melanoma - 8 cases (stage IIIB, IIIC), soft tissue sarcoma - 5 cases (large, recurrent or multiple). Control of leakage from the isolated limb in the general blood circulation system was carried out by the dynamic radiometry with  $^{99m}\text{Tc}$ -red blood cells (labeling in vivo) and precordial scintillation probe. Leakage was <6% (mean 1-2%). Perfusion was performed at mild hyperthermia.

**Results:** Overall response was recorded in 12 (92.3%) patients, CR - 3 (23.1%), PR - 9 (69.2%), SD - 1 patient. Limb salvage rate was 92,3%. One patient with large tumor had PR, but the tumor was still unresectable. Median follow-up - 12 months (range 2 to 25 months).

The local toxicity was slight (Wieberdink II). None of the patients had severe systemic toxicity.

**Conclusion:** ILP is a high efficiency and safe treatment modality (up to 92.3% of overall responses). Implementation of high regional chemotherapy is possible without significant local and systemic side effects.



## PRECLINICAL MODELS OF TUMOR-SPECIFIC CYTOTOXIC T LYMPHOCYTES IN SARCOMA PATIENTS

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Elena Signorino, Michela Muraro, Laura Castello, Sara Castiglia, Ivana Ferrero, Monica Gunetti, Alessandra Mandese, Katia Mareschi, Deborah Rustichelli, Fiorella Sanavio, Franca Fagioli

Stem Cell Transplantation and Cellular Therapy Unit, Pediatric Onco-Hematology Division, Regina Margherita Children's Hospital, Turin, Italy.

**Objectives stating concisely why the study was conducted:** Osteosarcomas and other sarcoma tumors are the most frequent bone tumors in adolescents and young adults. Progress has been made over the past 30 years in improving the outcome of high-risk sarcomas patients, but the 5-year overall survival rate remains at 20% or less for metastatic sarcomas. Although there are new experimental therapeutic strategies they have failed to significantly improve survival in this subset of patients.

The integration of adoptive immunotherapy strategies with chemotherapy and/or targeted therapies represent a reasonable and appealing innovative approach that has to be explored. Some recent clinical trials have confirmed the possibility of using autologous antitumor CTLs to control tumor growth.

The main aim of our study was to investigate the possibility of generating an *in vitro* tumor-specific targeted immunotherapy for bone sarcomas.

**Materials and Methods:** We isolated primary tumor cells from surgical biopsy, that were mechanically desegregated, maintained in culture and expanded *in vitro*.

We generated tumor specific CTLs through two stimulation dependent antigens, using the whole tumor cells as an antigen source. In particular, the irradiated tumor cells, were co-cultured with autologous dendritic cells, thus exploiting the capability of antigen presentation.

Subsequently, the CTLs were expanded in a antigen independent way with recombinant human IL-2 and anti-CD3 and a pool of irradiated PBMCs from three donors as a proliferative stimulation of CTLs. CTLs were expanded *in vitro* for several weeks.

**Results:** Sarcoma cells express specific MSCs markers: CD90, CD73, CD44 and CD105, and low levels of hematopoietic markers. Sarcoma cells express MHC I and maintain it after various culture passages and can thus be used as a target in *in vitro* tests to analyse CTL specificity.

The immunophenotype analysis of the subpopulation after CTL generation showed that CTLs were about 50% CD4 and CD8, less than 10% NK.

CTLs from sarcoma patients specifically kill autologous tumor cells.

This specificity was also seen with the ELISpot assay for INF-gamma release. This assay confirmed cytotoxic results: the release was higher using autologous cells as the target, and lower using commercial lines and allogeneic PB.

The fold increase of CTL expansion was good. This allowed us to expect a good number of cells in a clinical protocol of immunotherapy for sarcoma patients.

**Conclusions:** We managed to establish culture conditions from the surgical biopsy to generate and maintain sarcoma patients primary cells in culture

We generated efficient CTLs that are specific against those cells that were a source of antigens.

We had satisfactory *in vitro* expansion that provided a sufficient number of CTLs for clinical infusion.

Our findings are encouraging and support the design of adoptive immunotherapy clinical trials with autologous CTLs for sarcoma patients.

Cecilia Garofalo,<sup>1, 2</sup> Caterina Mancarella<sup>1, 2</sup>, Maria Cristina Manara<sup>1, 2</sup>, Chiara Donadei<sup>1, 2</sup>, Maria Serena Benassi,<sup>1</sup> Giordano Nicoletti,<sup>1</sup> Lorena Landuzzi,<sup>1</sup> Pier-Luigi Lollini,<sup>3</sup> Piero Picci,<sup>1</sup> and Katia Scotlandi<sup>1, 2</sup>

<sup>1</sup>Experimental Oncology Lab, Orthopaedic Rizzoli Institute, Bologna, Italy, <sup>2</sup>CRS Development of Biomolecular Therapies, Orthopaedic Rizzoli Institute, Bologna, Italy, <sup>3</sup>Department of Hematology and Oncologic Sciences "L. e A. Seragnoli", University of Bologna, Bologna, Italy.

**Background:** The IGF system has an important role in growth, tumorigenesis and cancer progression. In addition to the well-known role of IGF-1R, recent evidences have clearly demonstrated the importance of insulin and its receptor (IR) in both animal models and clinical studies. The isoform A of IR, which is usually overexpressed in cancer cells, may be stimulated by increased level of circulating insulin as well as IGF-2 and mediates non-metabolic effects, such as cell survival, proliferation, and migration. In addition, high levels of insulin, obesity and Type 2 diabetes are associated with increased risk for various malignancies. In this context, drugs aimed at reducing circulating insulin levels, such as metformin, have received attention as potential anti-cancer agents. Here we evaluated efficacy of metformin in Ewing sarcoma cells.

**Materials and Methods:** Effects on cell growth were evaluated by MTT assay. Effects on glucose up-take were assessed in the Ewing sarcoma TC-71 and SKNMC cell lines after treatments with metformin (10mM) and evaluation of fluorescent glucose up-take by microscopy. The antitumor activity of metformin was evaluated also in combination with conventional drugs doxorubicine, vincristine, actinomycin D and ifosfamide, which are the main drugs in the treatment of Ewing sarcoma.

**Results:** In vitro, metformin exhibited anti-proliferative activity, with IC50 values ranging from 6 to 21 mM. TC-71 cell line appeared the most sensitive to treatment, while 6647 and RD-ES cell lines were the most resistant ones. Time-dependent activation of AMPK, with subsequent variations in phosphorylation of the S6 protein and/or glucose uptake, indicated that conventional targets of metformin are affected. However, the variable efficacy of metformin in the different cell lines did not appear to be related to differences in these pathways, suggesting other still poorly defined mechanisms of action. Inhibitory growth effects were amplified when cells were grown in anchorage independent conditions. In addition, combined treatments of metformin with conventional chemotherapeutic drugs showed synergistic or additive effects, depending on drugs

**Conclusions:** These preclinical findings display a potential efficacy of metformin against Ewing sarcoma, particularly when combined with conventional drugs, thus supporting its possible use as adjuvant drug. (Grants: AIRC IG10452 to KS, AIRC to CG; MINSAN Finalizzata 2009)

## PROPOSAL ON UTILIZING LAUTENBACH SUCTION INSTILLATION SYSTEM TO PREVENT INFECTION IN MEGA PROSTHESES.

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*Dr's Richard Kyte & Franz Snyman*

*Division of Orthopaedic Surgery - University of the Witwatersrand - Johannesburg - South Africa*

The infection rate in Megaprosthetic replacements varies between 7 and 25% in different series, and for allograft reconstructions can be as high as 30-40%. We have been utilizing the Lautenbach suction instillation system in treatment of Bony and Prosthetic infections, by instilling high concentrations of antibiotic therapy into the wound bed, and combining the internal suction dressing effect. The purpose of this study was to compare our early infection rates, with the profilactic utilization of the Lautenbach system, to published infection rates.

We had 90 megaprosthetic reconstruction and musculoskeletal tumour patients, and 65 complex musculoskeletal trauma patients in the study, that was treated between 2004 and 2011, with profilactic Lautenbach irrigation.

Our infection rate in this study in the 44 patients with megaprosthetic, allograft and allograft prosthetic prosthesis composite reconstruction; were no early infections in the megaprosthetic category, and one each in the bulk allograft and allograft prosthetic composite category, amounting to 1,14%. No infections occurred in the 19 patients in the large soft tissue sarcoma category. (14 unrelated deaths) Our early results for infection prevention in these complex cases therefore compares very well to recent studies of between 7,7% (*Roggieri 2008*) and 47,8% (*Cummings 2010*).

The Lautenbach system was also utilized in complex musculoskeletal trauma patients with one infection in a grade 3 B open fracture, in the cohort of 65 patients, amounting to 1,5%. This again compares favourably to other studies where infection rates of 9-55% are reported.

Therefore the early results of our small inhomogenous cohort seem to support the utilisation of the Lautenbach suction instillation system as a profilactic measure to prevent deep infection in these complex cases.

Maria Teresa Marino<sup>1,2</sup>, Maria Cristina Manara<sup>1, 2</sup>, Andrea Grilli<sup>1,2</sup>, Massimo Serra<sup>1</sup>, Alessandra Carè<sup>3</sup>, Gianfranco Mattia<sup>3</sup>, Federica Sella<sup>1</sup>, Marco Alberghini,<sup>4</sup> Piero Picci<sup>1</sup>, Stefano Ferrari<sup>4</sup>, and Katia Scotlandi<sup>1,2</sup>

<sup>1</sup>Laboratory of Experimental Oncology, <sup>2</sup>CRS Development of Biomolecular Therapies, Orthopaedic Rizzoli Institute, Bologna, Italy; <sup>3</sup>Dept. of Hematology, Oncology and Molecular Medicine, Istituto Superiore Sanità, Rome, Italy; <sup>4</sup>Pathology Section, Musculoskeletal Tumors Chemotherapy Section Rizzoli Institute, Bologna, Italy

**Introduction:** MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules whose role as molecular biomarkers have been confirmed in several types of tumors. Recently, we have investigated miRNA expression profile in Ewing sarcoma defining a signature of miRNAs that was associated with a differential risk to disease progression. Of particular prognostic relevance appeared the expression of miR-34a and miR490-3p. In this study, we extended the analysis of miR34a expression in a larger cohort of patients homogeneously treated.

**Methods:** quantitative RT-PCR was performed by using Taqman Micro RNA Assay kit (Applied Biosystems) in 64 primary tumors of EFT (31 primary biopsy, 33 primary resection). Human normal stromal stem cells were used as calibrator. All tumor samples referred to Rizzoli Institute and were treated with high-dose chemotherapy according to ISG/SGIII protocol. Log rank ration, Kaplan-Meier survival curves and Cox multivariate analyses were used as statistical methods

**Results:** Expression profile of miR-34a was found to be significantly related to either EFS (p-value = 0.0165) or OS (p-value = 0.0136); Patients with the highest expression of the miR-34a had an event-free as well as a survival rate that was superior than 90%; on the contrary patients with the lowest level of expression had very high risk of progression. Multivariate analysis showed that miR-34a expression is as independent prognostic factor. Functional studies are on-going to establish its relationship with p53 signaling.

**Conclusions:** miR-34a expression was confirmed to be a strong predictor of outcome in EWS. Its routinely evaluation is strongly suggested to stratify patients according to risk, so sparing excessive long-term toxicity to EWS patients with good prognosis. (Grants: AIRC IG-10452 to KS, MinSan bando 2009; FS is a recipient of a fellowship from the Onlus Il pensatore: Matteo Amitrano per la ricerca su tumori ossei infantili)

# EFFECT OF THE ONCOLYTIC ADENOVIRUS DELTA-24-RGD IN AN IN VITRO AND IN VIVO OSTEOSARCOMA MODEL

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<sup>1</sup>Mikel San-Julián, <sup>1</sup>Blanca Vazquez-García, <sup>2</sup>Marta M. Alonso, <sup>3</sup>Lucía Marrodán, <sup>4</sup>Patricia Jauregui, <sup>2</sup>Enric Xipell, <sup>4</sup>Leire Urquiza, <sup>3</sup>Luis Sierrasesúmaga, <sup>4</sup>Fernando Lecanda, <sup>3</sup>Marta Zalacain, <sup>3</sup>Ana Patiño-García.

University Clinic of Navarra, <sup>1</sup>Dpt. of Orthopaedic Surgery, <sup>2</sup>Dpt. of Oncology, <sup>3</sup>Dpt. of Pediatrics; <sup>4</sup>Center for Applied Medical Research, CIMA – Pamplona - Spain

**Objectives and Background:** The conditionally replicative oncolytic adenovirus Ad5-Delta24RGD achieves tumor selectivity through a mutation in the Rb-binding CR2 region of E1A and presents enhanced tropism through integrin infection (RGD-4C modification of the fiber HI loop). Autophagic cell death is a type of programmed cell death that is an alternative to apoptosis; so that the development of autophagy-inducing treatments could be critical to improving the therapy for pediatric osteosarcoma. This study was designed to ascertain whether the combination of the oncolytic adenovirus Delta-24-RGD with cisplatin (CDDP) would result in an enhanced antitumor effect in vitro and in vivo in an in-house murine orthotopic osteosarcoma model.

**Materials/methods and results:** We performed in vitro studies using osteosarcoma cell lines that have been established from 4 of our osteosarcoma patients with metastatic disease: 531MII, 678R, 588M, and 598M.

Infectivity studies showed that all the cell lines were susceptible to the Delta-24-RGD infection ranging from 60 to 100% of infected cells at 25 MOI. Delta-24-RGD showed cytopathic effect and replication capacity in all cell lines. Viability assays showed that CDDP antitumor activity was synergistically enhanced by combination with Delta-24-RGD, lowering the IC50 for each of the drug in at least two logs of concentration. Treatment with CDDP resulted in G2-M cell cycle arrest that was overcome by the combination with Delta-24-RGD, indicating that addition of the virus sensitizes these cells to the drug antitumor effect. Of importance, combination treatment of Delta-24-RGD with CDDP resulted in autophagic cell death as shown by the electron microscopy and several autophagic biochemical markers such as LC3 conversion.

Orthotopic injection of 250.000 531MII cells in the tibial tuberosity resulted in development of tumors in >80% of Common gamma (γc)/Rag2/B10 animals. After tumor development, animals were randomized as +/-controls (no treatment), treated with CDDP (2 mg/Kg x 3 days/wk x 4 wk, i.p.), Delta-24-RGD (3.8x10<sup>7</sup> pfu once a wk x 3 wk, i.t.) or CDDP+Delta-24-RGD. Animals were followed with X-ray and at day 45 FDG-PET was performed, the animals were sacrificed and the tumoral lesions were analyzed by H&E staining, necrosis evaluation and IHC for different histologic and viral markers. Our preliminary data indicate that the virus has an important oncolytic activity in the tumoral lesions, which are significantly reduced compared to those from untreated mice.

**Conclusions:** Combination of the oncolytic adenovirus Delta-24-RGD with CDDP results in synergistic cytotoxicity through autophagic cell death. Our preliminary data suggest that exploiting autophagic cell death could provide new approaches to antitumor therapies. We have developed a valid orthotopic osteosarcoma model which we have used to validate the in vivo oncolytic activity of Delta-24-RGD.

# A NEW APPROACH IN THE CONSERVATIVE TREATMENT USING DAPTOMYCIN IN INFECTION CASES OF ENDOPROSTHESIS IN EAST EUROPEAN SARCOMA GROUP

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Nisichenko D.V., Grigorievskaya Z.V., Sokolovskiy V.A., Kubirov M.S., Sergeev P.S., Dmitrieva N.V., Aliev M.D.

N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

**The aim:** to evaluate the possibility of daptomycin in children and adults when performing operations endoprosthesis in bone tumors.

In accordance with the results of studies that were presented at the Annual Conference on Antimicrobial Resistance (2008 Annual Conference on Antimicrobial Resistance), daptomycin was effective in infections of the skin and soft tissues, caused by both MSSA, and MRSA strains of *Staphylococcus aureus*. Criteria for the application daptomycin with infections associated with the steel structure (stent) is not fully defined.

**Materials:** The investigation included 15 patients with cancer of bone, who underwent primary or repeat hip replacement, for the period from 03/2010 to 11/2010 in the Department of General Oncology NN Blokhin Research Institute. Min. age 10, max. 48 years (mean 18.6 years). Children under 12 used a dose 250mg/day; to 14 years 350mg/day. Adults 500mg/day. Duration of the course in prevention of infection (due to the high risk of infection implant bed) varied introduction of 8 to 26. In the treatment of infection rate ranged from 14 days to 36. At high risk of infection, we mean: the patients with resection of the proximal tibia, with a deficit of soft tissue to cover the endoprosthesis, an extensive skin necrosis in the postoperative scar, reimplantation. At 1/15 (6.5%) patient developed an allergic reaction in the form of urticaria.

For the treatment infection of the endoprosthesis bed daptomycin was used in 5 patients. In 3 out of 5 MRSE flora was detected in 2 out of 5 - MSSA. Ineffectiveness of daptomycin revealed only one out of five patients - 20% with the agent of MSSA. In this patient during surgery revealed osteomyelitis-spoke - MSSA, for a long time to receive preventive therapy daptomycin 500mg/day - without effect, the patient was removed implant, the defect is replaced by a spacer from the bone cement with gentamicin - pus from the wound continues to stand out; bacteriological crops - without any flora.

**Results:** In 10/15 (66%) cases, patients received a preventive daptomycin prevention of infection implant bed. None of the patients the infection was not detected during the observation period.

**Conclusion:** The use of the drug daptomycin in children and adults after using of tumor endoprosthesis, as a preventive antibiotic treatment is justified only for a group of patients at high risk of possible complications. Treatment of infections implant bed with daptomycin - effective, but requires further careful observation and analysis.

## FAMILIAL AGGREGATION OF URINARY TRACT AND BONE TUMOURS – SEARCHING FOR A SYNDROME: A CASE REPORT

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A. Frings\*, J.Geigl†, B. Liegl-Atzwanger\*\*\*, A. Leithner†

\*Department of Orthopaedics and Orthopaedic Surgery, Medical University of Graz, Auenbruggerplatz 5, 8036 Graz, Austria

†Institute of Medical Biology and Human Genetics, Medical University of Graz, Harrachgasse 21/8, 8010 Graz, Austria

\*\*\*Institute of Pathology, Medical University of Graz, Auenbruggerplatz 25, 8036 Graz, Austria

Medical family history is an important risk factor for various cancers and therefore further investigations needs to be done if a familial aggregation of cancer is observed. To address the hypothesized diagnosis Li-Fraumeni syndrome, we set out to investigate the case presented herein by molecular genetic analysis of the TP53 gene.

A 76-year-old Caucasian female was admitted to our department due to a tumour confined to her left proximal femur. The histologic examination confirmed grade 2 dedifferentiated chondrosarcoma. In the same year, the patient was diagnosed with a clear cell renal cell carcinoma. Medical family history revealed that her youngest brother started suffering from an invasive medium- to low-differentiated urothelial carcinoma of the bladder when he was 67 years old and finally died of an osteoblastic osteosarcoma (left femur) at age 69. Their mother had become ill due to renal cell carcinoma, as well, when she was 65 years old. Regarding the tumour spectrum presented herein, Li-Fraumeni syndrome was strongly considered as differential diagnosis. However, molecular testing did not reveal any pathologic alterations of the TP53 gene.

Based on current data, some minor changes found in the DNA sequence could be classified as polymorphism without pathologic significance, however, current data may be subject to changes. A genetic predisposition, perhaps due to other, currently unknown factors may still not be excluded. Regarding medical family history, the empirical risk for tumours has increased.

As the case herein reported implies, families with highly suspicious medical family history should be closely monitored to minimize disease-related morbidity. Clinicians should be aware of genetic syndromes like Li-Fraumeni syndrome as differential diagnosis – even if only to exclude the diagnosis.



G. Ulrich Exner<sup>1</sup>, MD, Charles E. Dumont<sup>1</sup>, MD, PhD, Pascal Schai<sup>2</sup>, MD

<sup>1</sup>Orthopaedie Zentrum Zurich ozz and <sup>2</sup>KS Luzern Wolhusen, Switzerland

**Introduction:** The advances of imaging modalities have importantly contributed to the improved outcome and survival of patients with malignant solid tumors. Better definition of resection planes and margins has allowed to replace amputation.

**Objective:** Having large experience in the CT-guided treatment of Osteoid-osteomas we have applied CT-based direction of resection margins in three different modalities.

### **Methods and Results:**

1°. Preoperative CT-guided insertion of K-wires to be used for orientation and as guides for the resection planes during definitive surgery (,conventional CT method')

*the day before or on the day of definitive surgery in the CT K-wires are inserted according to the planned resection planes. They are either left per- or subcutaneously. The cuts are performed by saw or osteotomy at the K-wire side averted to the tumor and guided by the K-wires*

2°. Preoperative CT-scan to be used for electronic navigation during surgery (neurosurgical Medtronic<sup>®</sup> system applied for tumor surgery, ,advanced CT-method')

*a CT scan of the region is performed with 4 stable marks inserted before surgery. While the patient is transferred to the operating theatre the CT data are loaded to the navigation system. When the patient is prepared for surgery the 4 inserted marks are used to synchronise the CT data in the navigation system with the patient. The ,navigation star' is calibrated and then used in the way traditionally used for navigation in joint replacement*

3°. Intraoperative use of a mobile CT combined with digital navigational (Medtronic<sup>®</sup> O-Arm, ,real time CT-method')

*The mobile CT-scanner is used as an image intensifier in combination with digital navigation during surgery. This is the ,easiest' application, but because of the cost of the O-Arm in the near future still unavailable in most set-ups.*

With these techniques precision of the planned resections has been reached in the order of a maximum deviation of 1 mm.

**Conclusion:** Computer assisted navigation is of great value in tumor surgery especially around the pelvis and around growth plates, when joint preservation is the goal.

## GAIT ANALYSIS AFTER RESECTION OF AN OSSSEOUS SARCOMA AND IMPLANTATION OF A PARTIAL PELVIC REPLACEMENT.

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Juergen BRUNS\*, Georg DEURETZBACHER\*\*

\* Dpt. of Orthop. Surgery, AGAPLESION Diakonieklinikum Hamburg, Germany

\*\* Laboratory for biomechanics, Dept. of Orthop. Surgery, University Hospital, Hamburg, Germany.

The analysis had been done in the laboratory for biomechanics.

Partial pelvic resection and implantation of a partial pelvic replacement (PPR) is one of the surgical procedures to cure a pelvic sarcoma.

In order to analyse the postop. gait with reproducible techniques, we performed as a pilot study a gait analysis in 6 patients suffering from a osseous pelvic tumor located in the P2-region.

**Material & methods:** For gait analysis the VICOM-system using video cameras and surface reflection markers had been used. Synchronously we recorded the ground reaction forces (GRF) and the surface-EMG data. Results from the patients treated side were compared with from the contralateral side and with those from healthy volunteers.

**Results:** We analysed 6 patients, 5 suffering from a primary bone sarcoma and one suffering from a loosened PPR. All received a partial pelvic replacement after tumor (P2-resection) resection or removal of the loosened PPR. The clinical Enneking score correlated well with the clinical gait and the data of the gait analysis.

The best patient (Enneking-score 28/30) did not show severe changes in the GRF, gait data, kinematics and EMG.

Patients with a medium result (Enneking-score 24-26/30) exhibited particularly in the kinematics of the pelvis and hip joint and in the EMG distinct changes compared to contralateral and volunteers.

The patient with the worst clinical score (Enneking-score 16/30) using a cane contralaterally) exhibited massive changes in all criteria.

**Discussion:** These pilot study demonstrates in concordance with the clinical score excellent results in patients with a good Enneking-score. Most of the patients (4) exhibited slight to moderate changes in all gait criteria. The worst gait data were seen in the patient with the worst Enneking-score.

Compared to a gait analysis in patients who had received a megaprosthesis into the distal femur those patients with a PPR demonstrated less changes in the knee and ankle joint and more changes in the hip and pelvic gait data.

Mohammad Shahid BSc MBBS MRCS Orthopaedic Registrar

Tom Saunders MBBS FY2

Mr Lee Jeys FRCS Consultant Orthopaedic and Bone Tumour Surgeon

Mr Rob Grimer FRCS Consultant Orthopaedic and Bone Tumour Surgeon

Royal Orthopaedic Hospital, Northfield, Birmingham, England, UK

**OBJECTIVES AND PURPOSE OF STUDY:** To present our results of the surgical management of symptomatic periacetabular metastases and develop an algorithm to guide management.

**MATERIALS AND METHODS:** Prospective study identified 81 patients, from 30,000 referrals between 1987 and 2010, with hip pain from metastases where periacetabular surgery was undertaken.

The diagnosis, lesion size, pelvic continuity, reconstruction type, WHO performance status, the time alive, pain, mobility and complications including implant failure were recorded.

**RESULTS:** The most common diagnosis was metastatic breast carcinoma (26 patients) followed by renal carcinoma (25 patients). The median survival of all metastases was 14 months, with no significant difference between categories (breast, renal, other,  $p=0.87$ ).

Operations performed with number in brackets; Total hip replacement (THR) with a 'Harrington type' acetabular reconstruction (32), Cemented THR (32), ice cream cone hemipelvic replacement (11), curettage and cementation (7), excision without reconstruction (6), tumour endoprosthetic replacement (1), THR with reconstruction with a ring or cement augmentation (9) and one patient required a palliative hindquarter amputation due to severe neurological pain.

There were significant differences between the longevity of reconstruction ( $\chi^2$ ,  $p=0.01$ ) with 5 failures of reconstruction which all occurred where cement supplementation was used to reconstruct the defect without reinforcement. There were no failures with reconstructions with tumour implants (EPR or coned hemipelvis placements).

Complications were hardware failure (8), dislocations (4), infection (2) & neurological injury (2), significant intra-operative haemorrhage (1), >2cm leg length inequality (1) and above knee DVT (2).

We present an algorithm for the treatment of periacetabular metastases.

**CONCLUSIONS:** Periacetabular metastatic lesions are challenging surgically, however, advanced techniques are more durable and likely to remain viable for the patients survival. We recommend an ice cream cone for pelvic discontinuity and Harrington rod reconstruction for severe bone loss. Smaller defects can be safely managed in a non tumour setting with standard revision hip techniques.

# LONG TERM FOLLOW UP OF COMPOSITE PROSTHESES AFTER PERIACETABULAR RESECTION.

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Delépine G<sup>1</sup>, Delépine F<sup>2</sup>, Alkhalaf S<sup>1</sup>, Cornille H.<sup>1</sup>

<sup>1</sup>Oncologic pediatric unit Raymond Poincaré Hospital Garches France

<sup>2</sup>Clinique du parc impérial 28boulevard du tzarevitch 06045 Nice France

**Objectives:** Internal hemipelvectomy followed by acetabulum reconstruction is a very demanding procedure and 5 year life expectancy of the patients rarely exceeds 50%. For these reasons few reports give long term results of reconstructive procedures. We want present here the results of patients with hand on innominate prosthesis with total hip prosthesis.

**Materials and methods:** The hand on innominate prosthesis described in 2003 (Sarcoma 2003 7,19-27) is made of a titanium cup, a set of long titanium screws and 2 or 3 packs of antibiotics loaded cement.

Between 1990 and 2007, 84 patients with for peri acetabular bone sarcoma (40) or metastases (44) have been treated by internal hemipelvectomy followed by this reconstructive procedure. Only 23 survivors (20/40 sarcoma and 3/44 metastases) could be followed more than 5 years. ). The histology of tumors of these 23 patients included chondrosarcoma in 8 patients, osteosarcoma in 5, Ewing's in 5, , MFH in 1, anaplastic sarcoma in 1, renal cell carcinoma in 2, thyroid in 1,. Resection included 4 zone 2, 6 zone 2+3, 9 zones 2+1, 3 zones 2+1+4, and 1 zones 1+2+3.

**Results:** The mean follow up of these patients is 13,5 years (range 63 to 240 months). A lot of postoperative complications have been observed; 1 deep infection, 6 hip prosthesis dislocation (26%), neurologic palsy (2). Late complications included 2 deep infection, 6 polyethylene wear and 7 loosening (5 iliac, 2 femoral). 10 patients (43 %) had to be re operated. The rate of orthopedic complications is significantly correlated with the topography of the resection : loosening of the iliac reconstruction was observed only after resection of zone 1

To evaluate the function, we used the musculoskeletal tumor society system derived from Enneking. For overall evaluation numerical rating was used for better comparison of alternative method. Each of these seventh variables was assessed on a five point scale, giving a maximum score of 35 points which was recorded as 100 %. As the aim of the study was to evaluate the orthopaedic result of the implants we take in account the last score of patient with local control. The mean functional result, rated according modified Enneking's grading system, was 80%. This result is similar to those described in the literature for custom made innominate prosthesis and better than those of published alternative reconstructive procedures.

**Conclusions:** The immediate advantages and the durability of such procedure plea for using it extensively after acetabulum resection of zone 2 and 3 where we did not observed loosening of the iliac reconstruction. Such a procedure can also be used after total iliac wing resection even when including zone 4. but in this location loosening is frequent and pleas for reinforcing the reconstruction with the head and neck of femur when there are free of tumor.

Martin Wessling<sup>1,4</sup>, Mirko Aach<sup>1,2</sup>, Arne Streitbuerger<sup>1</sup>, Helmut Ahrens<sup>1</sup>, Georg Gosheger<sup>1</sup>, Jendrik Hardes<sup>1</sup>, Carsten Gebert<sup>1,3</sup>

- 1) Department of orthopaedic surgery, University Hospital Muenster, Albert-Schweitzer-Str. 33, D -48149 Muenster
- 2) Department of Trauma Surgery and spinal chord injuries, University Hospital Bergmannsheil Bochum, Buerkle-de-la-Camp-Platz 1, D-44789 Bochum
- 3) Department of tumour and revision surgery, Orthopaedic Hospital Volmarstein, Lothar-Gau-Str. 11, D-58300 Wetter
- 4) Department of Orthopaedics and Trauma Surgery, University Hospital of Bonn, Sigmund-Freud-Strasse 25, D-53105 Bonn

**Objective:** Up until now, no consensus has been reached whether there is a need for reconstruction in supraacetabular defects or not. As a result, no universal procedure has been established yet. This retrospective study was initiated to analyse clinical and functional outcome of pelvic ring reconstruction using a traditional biological reconstruction versus a new material combination.

**Material and methods:** This study retrospectively evaluates 39 (w=20/m=19) patients with a mean age of 30,5 years (8,2y to 78,9y), who had undergone supraacetabular tumor resection (plb and plc according to Enneking). Indications for surgery where as follows: Ewing sarcoma n=25, osteosarcoma n=4, chondrosarcoma n=5, other n=5. The pelvic ring was reconstructed biologically (n= 11; allograft n=3, autograft n=8) or by a combination of polyaxial screws and titanium rods augmented with PMMA (n= 28).

**Results:** The mean follow-up was 48,8 month (3 to 139,5). The mean operation time was 244 min(biological) versus 269 min (mechanical). Mean time to mobilisation with weight bearing was 27,8 weeks (biological) versus 3,7 weeks (mechanical). The patient 5-year overall survival rate was 77.2%. The 5-year survival rate based on the type of reconstruction was 69.3% (biological) and 79.6% (mechanical), respectively.

Wound healing problems where observed in 9 cases (biological n=1, mechanical n=8), deep infection in 5 cases (biological n=2, mechanical n=3). Local recurrence was observed in 4 cases (biological n=3, mechanical n=1). The biological reconstruction needed to be revised in 4 cases (36.4%), the mechanical reconstruction also in 4 cases (14.3%). The mean MSTS-score was 70.0% (biological=69.3%, mechanical=70.3%).

**Conclusion:** Both types of reconstruction presented here show an adequate functional outcome with relative low complication rates. Main advantage of the non-biological reconstruction is the potentially early mobilisation.

# CURETTAGE OF TUMOR LESIONS OF THE PELVIS AND SACRUM WITH THE AID OF CRYOSURGERY FOR BLOOD SPARING AND ADJUVANT EFFECT

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Guido Scoccianti, Domenico Andrea Campanacci, Giovanni Beltrami, Filippo Frenos, Rodolfo Capanna

Department of Orthopaedic Oncology, AOU Careggi, Firenze, Italy

**OBJECTIVES:** Intralesional curettage of benign aggressive tumors or metastatic lesions in the pelvis and sacrum can be a challenging procedure when dealing with wide lesions or with tumors at high risk for massive bleeding. To reduce bleeding and to obtain an antitumoral effect on surgical margins, we began to use cryosurgery as an aid during removal of the lesion, which is progressively freezeed and curetted, and as an adjuvant treatment after curettage on the remaining walls of the cavity. A retrospective evaluation of 10 cases treated with this technique was performed to verify its efficacy and safeness.

**MATERIALS AND METHODS:** In the last five years we performed 10 surgical procedures of intralesional excision of bone tumors in the sacrum and pelvis with the intraoperative aid of cryosurgery.

Histology of the tumor was: metastatic lesion from renal cell adenocarcinoma in 4 cases, metastatic lesion from hemangiopericytoma in 1, giant cell tumor in 1, aneurysmal bone cyst in 1, schwannoma in 1, chondrosarcoma in 2 cases. Location of the tumor was: sacrum in 3 cases, sacroiliac area in 2, periacetabular in 3, ileopubic ramus in 1, ischium in 1.

Age of the patients ranged from 19 to 77 years (average 56). Freezing was performed using cryoprobes reaching a temperature of -150°C. Size and number of probes varied according to size and location of the lesion. According to location and characteristic of the lesion, the defect was filled with cement or left empty.

**RESULTS:** Average duration of surgery was 3.6 hours (2.15–6). Cumulative number (intraoperative and postoperative) of blood transfusions per patient ranged from 0 to 15 (average 3.8). In one patient control of bleeding was particularly difficult and the patient received 15 blood units; in the remaining 9 patients average number of blood transfusions was 2.5. In these cases, at intraoperative haemogasanalysis and postoperative blood exams, HGB value never fell under 7 g/dL.

No skin necrosis was encountered. No deep infection and no neurovascular damage occurred.

Follow-up ranged from 0 to 47 months (average 19.5). Two patients affected by metastatic disease died 14 and 15 months after surgery for systemic disease. In the 7 patients with follow-up longer than 1 year no local recurrence or progression (in the case of schwannoma a partial curettage was performed) was observed,

**CONCLUSIONS:** Cryosurgery as an aid during curettage of bone tumors of the sacrum and pelvis is a useful tool to decrease bleeding in a high-risk surgery. Use of cryoprobes to freeze tumoral tissue resulted in limited bleeding. The absence of complications showed the safeness of the technique. Effect of cryosurgery on surgical margins in intralesional excisions need a longer follow-up and wider series to be evaluated.

# TWO STAGED REVISION OF SEPTIC FAILURE OF MASSIVE ALLOGRAFT RECONSTRUCTION AFTER TYPE II-III PELVIC RESECTION WITH CUSTOM MADE PROSTHESIS: A CASE REPORT

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M. Ayvaz, S. Bekmez, M. Tokgozoglu (Ankara, Turkey)

Reconstruction of defects after plevic sarcoma resection with massive structural allografts is the choice of treatment in young patients with high functional demands. High risk of infection is one of the most important factors affecting the outcome of massive allograft reconstruction. Revision afterseptic failure is a challange for surgeon and even amputation may be an option.

**Case Report:** A 29 y.o. male patient, with complaints of pain and a mass in his thigh, in an outcenter clinic, had a diagnosis of chondrosarcoma after biopsy. Tumor excision had been performed for two times, afterwards, he had been referred to our clinic because of recurrence of the tumor. After clinic and radiographic evaluation, Type II + III hemipelvectomy and reconstruction with massive structural pelvic allograft was performed, five years ago, with the diagnosis of recurrent chondrosarcoma. Allograft resorption and drainage from the incision was found in the fourth year follow-up. Multiple debridements, spacer with antibiotic loaded cement and Vacuum assisted closure implementations was performed. In deep cultures, Klebsiella pneumonia was isolated, so parenteral antibiotics was admitted for 6 weeks, parenterally. After improvement of clinic and serologic markers, reconstruction with custom-made pelvic prosthesis was performed, fifteen months ago. Resultant soft tissue defect is closed with rectus abdominis local flap by plastic surgeons. After one year follow-up, infection markers were normal and MSTS score was 20 (good).

Higher rates of mechanical insufficiency and infection (up to 50% in the literature) has been reported after reconstruction with structural bone allografts in the treatment of pelvic sarcoma. In case of failure of reconstruction with allografts,two stage revision with custom made pelvic prosthesis can be a good option



L. van der Heijden MSc<sup>1</sup>, A.P. van Noort-Suijndorp MD<sup>2</sup>, M.A.J. van de Sande MD PhD<sup>1</sup>, A.H.M. Taminiau MD PhD<sup>1</sup>, B.J. van Royen MD PhD<sup>3</sup>, P.D.S. Dijkstra MD PhD<sup>1</sup>

1. Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, the Netherlands
2. Department of Orthopaedic Surgery, Vlietland Hospital, Schiedam, the Netherlands
3. Department of Orthopaedic Surgery, VU University Medical Center, Amsterdam, the Netherlands

**Objectives:** Surgical management of giant cell tumors of the sacrum (2-8% of all GCT) is challenging because of (usual) late discovery, large size, sacral nerve root involvement and spinal instability. Only small case series on intralesionally treated sacral GCT have been published thus far; optimal treatment for sacral GCT remains subject of debate. The purpose of the present study was to evaluate mid-term clinical outcomes after intralesional excision of sacral GCT.

**Methods:** From 146 consecutive patients treated for GCT between 1994 and 2009 at a tertiary referral center, we retrospectively evaluated all 15 patients with sacral GCT. One patient was excluded due to inoperability (extensive presacral soft tissue involvement). Thus, 14 patients (6 male, 8 female, mean age 38 years, range 14-66) were included; 12 patients underwent primary surgery and two were referred for treatment of local recurrence. Mean follow-up was 88 (5-209) months; no patients were lost to follow-up.

**Results:** Preoperative complaints were pain (n=14), sensory impairment (n=3), bladder dysfunction (n=2), rectal dysfunction (n=2) and progressive neurologic deficits (n=2). All patients underwent selective arterial embolization and curettage. Three patients had additional partial excision of the anterior sacral wall. Resection was not indicated since the lesion was localized in S1 and lower segments (12 patients) and distal from S2 (2 patients). Reconstruction was performed through bonegrafting in 6 patients and posterior spinopelvic fusion in 2 patients (1 with bonegrafting); no reconstruction was needed in 6 patients. Three patients received neoadjuvant interferon- $\alpha$  and one bisphosphonates.

**Oncological outcome:** Seven patients (50%) developed a local recurrence after a median of seven months (range 3-139). Increasing the surgical margin by partial excision of the anterior sacral wall showed a reduced recurrence risk (1/3). Recurrence rate was also lower after neoadjuvant IFN- $\alpha$  (1/3). Recurrences were treated with a combination of re-curettage (n=6), additional partial excision (n=2), adjuvant radiation therapy (n=3), bisphosphonates (n=1) and radiofrequency ablation (n=1). Reconstruction was performed through posterior spinopelvic fusion and bonegrafting in three and bonegrafting alone in one patient; no reconstruction was needed in three patients. Three patients developed a second recurrence. Two patients died from extensive tumor growth and distant metastases at 5 and 41 months after initial surgery; one developed multiple recurrences.

**Surgical outcome:** Postoperatively, complaints of pain resolved in eight patients; rectal dysfunction resolved in two; and bladder dysfunction remained in two. Sensory impairment was improved in two patients and remained in one. Four patients developed a (partial) cauda syndrome which eventually resolved in two. Other postoperative complications were delayed wound healing (n=1), wound infection (n=1), failure of instrumentation (n=1) and radiation induced menopause (n=1).

**Functional outcome:** Mean Musculoskeletal Tumor Society (MSTS) score was 25 (15-29) at final follow-up. MSTS scores were highest for 6 patients without local recurrences (21-29) and lowest for 3 patients with cauda equina syndrome (15-21). Walking distance was normal in 10 patients and limited in one. One patient is wheelchair bound. Two patients had progressive neurological deficits and deteriorated function shortly before death.

**Conclusions:** Overall local recurrence rate after intralesional excision was high (7/14). This was notably higher after curettage alone (5/7), suggesting that adjuvant treatment may be desired to obtain immediate local control of sacral GCT. This could result in less complications and superior functional outcome, as was demonstrated in patients without local recurrences. Local recurrence risk may be reduced by wider surgical margins (e.g. anterior wall excision), neoadjuvant IFN- $\alpha$  or external beam radiation for residual or recurrent disease.

Daniel Soares, Vânia Oliveira, Luciana Leite, Luís Costa, Pedro Leite, Pedro Cardoso

Department of Orthopaedics  
Centro Hospitalar do Porto – Hospital Geral de Santo António  
Oporto, Portugal  
www.chporto.pt

#### Introduction and Objectives

Giant cell tumor of bone is the sixth most common primary osseous neoplasm accounting for about 5 percent of all primary bone tumors. It has a peak incidence in the third decade of life and, although being considered a benign lesion, this type of tumor is locally aggressive and tends to recur after resection. Giant cell tumors typically presents as an eccentric lytic lesion with ill-defined borders and in the absence of perilesional sclerosis.

More than 75 percent of giant cell tumors are located at the articular ends of long bones. Indeed, pelvic involvement, with the exception of the sacrum, is rare, and particularly the involvement of the ischium represents only 0.5 percent of all giant cell bone tumors.

Treatment options include curettage alone, wide resection or excision-curettage, with or without radiotherapy, and depend on the stage of the disease, its location and expectations of the patient.

The purpose of this presentation is to report a rare case of a giant cell tumor of the ischium.

**Case Report:** The authors present an interesting case of a 30 year-old male with complaints of persistent hip pain after trauma during sport activity. Physical examination and laboratory data were not remarkable but the radiographs showed an ill-defined expansile and lytic lesion of the left ischium, extending into the acetabulum.

Additional studies with CT-scan and MRI confirmed a destructive, lytic lesion with origin in the left ischium extending into the posterior pillar of the acetabulum and involving the adjacent soft tissues, with exuberant vascularization. CT-guided biopsy revealed a giant cell tumor and the patient underwent surgery after previous angiography for selective arterial embolization in order to reduce tumoral vascularization. An excision-curettage procedure was chosen with resection of the entire soft tissue component and the left ischium. In the acetabular extension of the tumor it was performed an extensive curettage followed by phenolization and cement-filling of the cavity. The patient also received adjuvant radiotherapy.

Histologic review of the excised lesion confirmed the diagnosis of giant cell tumor.

One year after treatment he remains asymptomatic and without evidence of recurrent disease.

**Discussion:** Giant cell tumor of the ischium is rare and often of difficult diagnosis because the clinical presentation may be easily confused with low-back pain or muscle strain.

Due to its location there is usually some delay in the appearance of symptoms. This fact allows them to reach quite large dimensions until the time the diagnosis is made.

In the reported case the authors were dealing with a stage 3 tumor, as it was described by Enneking, because it involved the surrounding soft tissue and threatened the integrity of the acetabulum. These features required the resection of the entire soft tissue component as well as of the left ischium associated with curettage and cementation of the acetabular extension. This was done to avoid endangering the stability of the hip and because of the potential comorbidity associated with supplementary reconstruction procedures. Radiotherapy was also used as a way to decrease the risk of local recurrence.

In conclusion, it must be stressed out that a clinician must maintain at all times a certain degree of suspicion when a young patient has pain that does not resolve. Furthermore, because of the potential problems that pelvic giant cell tumors impose, one should keep in mind that treatment must be individualized, depending on the stage of the disease, its location, and the expectations of the patient.

# CLEAR CELL SARCOMA OF THE GLUTEAL REGION WITH A LARGE INTRAOSSEOUS PORTION IN THE ILIAC BONE

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C. Wibmer, MD<sup>1</sup>, B., E. Fröhlich-Sorger, MD<sup>1</sup>, P. Sovinz, MD<sup>3</sup>, W. Maurer-Ertl, MD<sup>1</sup>, A. Leithner, MD<sup>1</sup> B. Liegl<sup>2</sup>.

<sup>1</sup>Dept. of Orthopaedics and orthopaedic Surgery, <sup>2</sup>Institute of Pathology, <sup>3</sup>Division of Paediatric Haemato-Oncology, Medical University of Graz, Austria

**Objectives:** Clear cell sarcoma (CCS), also called malignant melanoma of the soft tissue, is a rare entity (1% of all soft tissue sarcomas) with a predilection of tendons and aponeuroses, an incidence peak around the 3rd decade, and an often fatal prognosis due to lymphatic metastases and lack of effective systemic therapy. Recent studies discuss the similarities between EWSR1-rearrangement positive (EWSR1+) and negative (EWSR1-) CCS and metastatic malignant melanoma, and possible future therapy-options with the same multikinase or tyrosinekinase inhibitors. We present the rare case of a CCS with a large intraosseous portion in the pelvic bone.

**Case report:** A 18-year-old female presented at the authors department in January 2012 with a tender, fast-growing mass in the right gluteal region. MRI and conventional radiographs revealed an osteodestructive process of max. 3 cm in the iliac bone and a soft tissue mass measuring 7.5 cm, with contrast enhancement and central necrosis. The radiologic differential diagnoses were Ewing's sarcoma, osteosarcoma or soft tissue sarcoma. Staging (CT-scan) revealed local lymphnode metastases, but no distant metastases. Biopsy sampling showed round to oval spindle cells arranged in nodules, in between rough collagen bands, positive for S-100 and Vimentin, negative for Pancytokeratin, EMA, SMA, Desmin, CD99. Only few, isolated cells showed positivity for Melan A. FISH analysis revealed a rearrangement 22q12 confirming the diagnosis of a clear cell sarcoma of soft tissue. A wide resection, including partial pelvic resection, as well as lymphnode resection was performed. Reconstruction included arthrodesis of the remaining sacroiliac joint with cancellous bone graft and canulated screws.

Histopathology revealed a malignant mesenchymal tumor arranged in nests and fascicles. The tumor cells were polygonal/epitheloid and spindle cell shaped with abundant eosinophilic to clear cytoplasm. The nuclei were vesicular with prominent nucleoli. The nests were partly surrounded by fibrous septa with wreath-like multinucleated giant cells. An area contained melanin pigment. Necrotic areas and up to 9 mitoses per 10 HPF were seen.

Immunohistochemistry showed a significant positive reaction with AB against S100, HMB 45 and Melan A. Mutational analysis did not demonstrate a *BRAF* V600E mutation nor other mutations in EXONS 11 and 15 of the *BRAF* gene.

A resection with clear margins was confirmed but 4 out of 7 of the resected iliac lymphnodes revealed metastatic disease. The interdisciplinary tumorboard decided for adjuvant local irradiation including the lymph drainage region and adjuvant systemic therapy with a tyrosine-kinase-inhibitor.

**Conclusions:** An osteolytic lesion in the iliac bone in combination with a soft tissue mass in an adolescent, would lead to other, more frequent differential diagnoses than CCS. In this case of CCS a possible origin in the bone may be discussed, although the radiology displayed the main part of the mass in the soft tissues.

N. FABBRI, G. Bianchi, M. De Paolis, P. Ruggieri, M. Mercuri

Istituto Ortopedico Rizzoli, Bologna, ITALY

**Objectives:** Durable acetabular fixation is a challenging problem after radiotherapy for pelvic malignancy. Acrylic cement is a short-term satisfactory solution but is associated with significant risk of failure at follow-up longer than 5 years. Porous tantalum has been successfully used during the last decade in complex joint revision surgery and its great potential for osseointegration makes it an ideal material for use in biomechanically difficult situations such as radiation-induced osteonecrosis. Goal of this study is to analyse the results obtained using a porous tantalum cementless acetabular component in patients undergoing total hip replacement after radiation therapy.

**Materials e Methods:** It is a retrospective study of 8 patients managed using an uncemented porous tantalum acetabular component for primary implant (6 cases) or revision surgery of a previously failed total hip arthroplasty (2 cases) after radiation therapy; 5 females and 3 males, average age 49 years (26-76 yrs). The cause for radiation therapy was a primary musculoskeletal neoplasm of the pelvis in 5 cases and an hematologic condition /metastatic cancer in 3 cases. At the time of surgery, none of the patients presented evidence of clinical activity of the underlying disease at a minimum follow-up of 2 years (2-12 years). The 2 revision cases consisted of one case of aseptic loosening and one case of deep infection, at 3 years and 1 year respectively from previous surgery. Deep infection has been treated by staged revision. In 2 cases, the porous tantalum acetabular component has been associated with an "augment" to fill a segmental periacetabular defect and support the cup. Minimum follow-up after implantation of the porous tantalum socket is 2 years. in all the cases, mean follow-up is 3 years (2-5.5 yrs).

**Results:** In none of the cases there was local recurrence. There has been 1 case of recurrent hip dislocation requiring further surgical management. There is no clinical nor radiographic evidence of acetabular or femoral loosening at the most recent follow-up. Implant is well functioning and stable in all cases. These results are very promising and are related to the great potential for osseointegration of porous tantalum.

**Conclusions:** Porous tantalum has been very satisfactory at short term follow-up, demonstrating reliable capability to obtain biologic fixation after radiation therapy. A longer follow-up is necessary to identify later potential failures.

## INVERTED “U” APPROACH FOR ONCOLOGIC RESECTIONS AROUND THE PELVIS. COMPLICATIONS REPORT

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*GALLI SERRA MARCOS*

**Background:** Limb-sparing surgery for tumors around the pelvis is complex and associated with a high morbidity (20 to 80 %). The extended sacroiliofemoral or ilioinguinofemoral (triradiate) approach is frequently used in these complex surgeries in spite of the high incidence of local complications reported. The aim of the following study was to develop an alternative to this classic approach, (i.e. a variant of surgical exposure) described as an inverted “U” with a distal base over the iliac crest, and to report the incidence of local complications.

The hypothesis is that this surgical exposure preserves the skin vascularity in the above mentioned region thus reducing local wound complications.

**Methods:** From 2004 to 2008 we performed eight hemipelvectomies for different musculoskeletal tumors (four chondrosarcomas, five metastatic lesions, two from myelomas one from thyroid adenocarcinoma, and 1 dysplasia epiphysealis hemimelica. We describe the surgical technique.

**Results:** The margins obtained were classified as “wide”. The length stay at the hospital in average was 7.1 (10-4) days. With this approach we had no wound dehiscence or superficial infections. One patient presented a complication (partial necrosis of the wound) requiring an irrigation and debridement procedure.

**Conclusions:** The inverted U approach appears as an alternative in selected cases to the classical extended sacroiliofemoral or ilioinguinofemoral (triradiate) approach for hemipelvectomies. The incidence of local complications is lower and allows for a correct exposure of the pelvis without compromising the resection margins.

**KEY WORDS:** Approach. Pelvis. Complications. Inverted U. Limb salvage. triradiate approach.

Yang-Guk Chung, Yong-Koo Kang, Won-Jong Bahk, An-Hi Lee\*, Jung-Mi Park\*\*, Chan-Kwon Chung\*

Department of Orthopedic Surgery, Clinical Pathology\*, Radiology\*\*, College of Medicine, The Catholic University of Korea, Seoul, Korea

**Objectives:** Surgical treatment of malignant pelvic bone tumors is a difficult problem due to complex anatomy, delayed presentation and limited imaging information even with various preoperative imaging studies and intraoperative fluoroscopy. A computer-assisted navigation system may be helpful especially in juxta-acetabular or juxtасacral tumor resection for preserving hip joint or neural structure, which will provide functional excellence. We evaluated the result of our early experience of pelvic tumor resection using computer-assisted navigation system.

**Materials and methods:** Four patients with juxta-acetabular malignant bone tumor and one patient with posterior iliac bone tumor underwent surgical resection with the aid of computer-assisted navigation system. There were one high grade chondrosarcoma, four metastatic carcinomas from thyroid follicular adenocarcinoma, laryngeal ca or malignant peripheral nerve sheath tumor. After histologic diagnosis, the resection plans were set with through analysis of all preoperative imaging studies. The nearest distances from tumor margins to acetabulum or sacral foramen were 12-20 mm. Tumor resection were carried out with the guidance of three plane localizations of cutting points provided by computer-assisted navigation with a mobile multidimensional imaging system (O-arm, Medtronic co.) The achieved surgical margin and evidence of local recurrence were evaluated. The mean follow up periods was 19.2 months (12-28 months)

**Results:** Minimum 5 mm surgical margins were obtained in four juxta-acetabular malignant pelvic bone tumors (5-11 mm). There was no evidence of local recurrence in four patients with 13-28 month follow up. One latest patient with metastatic malignant peripheral nerve sheath tumors involving right posterior iliac bone and SI joints revealed 4 mm clear margin with the preserved lumbosacral plexus function postoperatively. However, one new metastatic focus was developed near the resection margin of posterior ilium 4 month after initial operation.

**Conclusion:** Precision of tumor resection with narrow surgical margin using Computer-assisted navigation system allowed joint preserving surgery in four juxta-acetabular malignant bone tumors and preservation of neural structures in one juxta-sacral malignant bone tumor.

# OSTEOSARCOMA IN ASSOCIATION WITH HODGKIN'S LYMPHOMA IN A 15-YEAR OLD MALE PATIENT BORN IN A FAMILY WITH HIGH TUMOR BURDEN

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Woltsche N<sub>1</sub>, Friesenbichler J<sub>1</sub>, Maurer-Ertl W<sub>1</sub>, Urban C<sub>2</sub>, Müller E<sub>2</sub>, Leithner A<sub>1</sub>

<sup>1</sup> Department of Orthopedic Surgery, Medical University of Graz, Austria

<sup>2</sup> Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria

**Introduction:** The coincidence of malignant lymphoma and osteosarcoma with or without genetic background is rarely observed. Li-Fraumeni syndrome is a cancer predisposition syndrome associated with a diversity of malignancies including sarcomas and also hematopoietic malignancies like lymphomas. Two manifestations can be distinguished: classic Li-Fraumeni syndrome and Li-Fraumeni-like syndrome, which does not share all characteristics listed for classic Li-Fraumeni syndrome. Only 8 to 22% of patients suffering from Li-Fraumeni-like syndrome show a detectable p53 mutation.

**Case presentation:** We present a 15-year old male patient, who was diagnosed a nodular-sclerosing Hodgkin's lymphoma at the beginning of 2011. Under the initiated polychemotherapy (OEPA/VEPA) a complete remission could be achieved. Within a reuptake examination for progression of the chemotherapy's second block in April, the patient reported pain in his left knee dependent on activity. Plain radiographs and magnetic resonance imaging revealed an osteodestruction in the left distal femur. A biopsy was inconclusive. Three months later, a progression of the osteodestruction was shown by imaging procedures and an open re-biopsy revealed an osteoblastic osteosarcoma. His relations in first and second degree increasingly developed solid tumors, for instance leukemia, cervical carcinoma, colon carcinoma and bronchial carcinoma. A Lynch syndrome was excluded by immunohistochemical detection of the DNA repair enzymes MLH-1, MSH-2, MSH-6 and PMS-2. A loss of activity of these enzymes could not be shown in the extracted tissue. A p53 mutation associated with Li-Fraumeni syndrome was excluded by genetic analysis of a blood sample.

**Discussion:** In the past, the development of osteosarcoma as second malignancy after childhood malignancies was attributed to the carcinogenic effects of treatment. The synchronous diagnosis and the family's high tumor burden in this case suggest a genetic predisposition – however, evidence has not yet been provided. In consideration of his family's background the patient could suffer from Li Fraumeni-like syndrome.



# MULTIFRACTAL ANALYSIS ON MICROSCOPIC IMAGES AS A EFFECTIVE TOOL IN THE CLASSIFICATION OF METASTATIC BONE DISEASE

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J. Sopta\*, J. Vasiljevic\*\*, N. Lujic\*\*\*, G. Tulica\*\*\*\*, D. Ristic\*\*\*\*\*, J. Bokun\*\*\*\*\*, V. Mijucic\*\*\*\*\*

\*Institute for Pathology, Faculty of Medicine, University of Belgrade, Serbia

\*\* Institute "Mihajlo Pupin", University of Belgrade

\*\*\*Institute for Surgical and Orthopaedic Diseases "Banjica", Belgrade, Serbia

\*\*\*\* Clinic for orthopaedic surgery, University of Belgrade, Clinical centre, Belgrade, Serbia

\*\*\*\*\* Institute for Oncology and Radiology, Belgrade, Serbia

**Objectives stating concisely why the study was conducted:** In this study an image classification method based on the multifractal analysis (MF) is described. This method can be applied as an additional and objective tool in identification of primary cancer in cases of metastatic bone disease, as well as in decreasing of the subjective factor and error probability. This research was directed to find differences in parameters of multifractal analysis between three types of primary cancer which produce bone metastases: renal cell, breast carcinoma and lung carcinoma.

**Materials and Methods:** The method is tested on a 1050 cases of metastatic carcinoma into the bone who were diagnosed on the Institute of Pathology. MF analysis can be applied to gray-level images, in general. The shape of segmented objects within an image can be described by analyzing binary images (black and white).

**Results:** This study shows that parameters of MF are significantly different for all three investigated groups of tissue images. The accuracy of all three types of cancer was higher than 73%. The highest accuracy (78.38%) and the highest specificity (85.71%) were confirmed in MF prediction for lung carcinoma. The most sensitive MF (sensitivity 68.29%) was in cases of breast carcinoma. Importance of parameters in classification of metastatic cancers was also classified:  $\alpha_{\max} 100.000$ ,  $f(\alpha)_{\max} 81.129$ .

**Conclusions:** The accuracy of all three types of cancer was higher than 73%. According to that we can conclude that using this method we can postulate primary localisation of metastatic bone carcinoma.

# GENOTYPING OF CANDIDATE SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATED WITH OSTEOSARCOMA IN A GROUP OF PATIENTS WITH VARIOUS BONE TUMORS

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<sup>1</sup>Naumov V.A., <sup>1</sup>Generozov E.V., <sup>2</sup>Kushlinskiy N.E.

<sup>1</sup> Research Institute of Physico-Chemical Medicine MBA RF

<sup>2</sup> Russian N.N.Blokhin Cancer Research Center RAMS

**Objectives:** Osteosarcoma (OS) is a bone malignancy occurring primarily in adolescents and young adults. With the exception of rare syndromes, little is known about genetic predisposition to sporadic form of OS and other bone malignancies. One of the recent large scale studies [Mirabello et al., BMC Cancer 11:209, 2011] demonstrated significant association between OS and single nucleotide polymorphisms (SNPs) in genes involved in the regulation of bone growth and DNA repair. Practically no data are available about possible association of SNPs with other types of bone tumors.

**Methods:** 66 bone tumor patients (35 males, 31 females, age 16 - 74) receiving treatment in the Russian N.N.Blokhin Cancer Research Center RAMS: 26 OS, 23 chondrosarcoma, 12 giant cell tumor, 4 Ewing's sarcoma, 1 malignant fibrous histiocytoma, 1 schwannoma and 1 enchondroma cases - were enclosed in this study. 96 age- and sex- matched cancer-free healthy individuals were comprised a control group. Genomic DNA was extracted from peripheral blood. Genotyping of 5 candidate SNP's located in genes involved in bone formation: growth hormone 1 (GH1) gene (rs7921), insulin-like growth factor 1 (IGF1) gene (rs7956547), gonadotropin-releasing hormone 2 (GNRH2) gene (rs3761243), fibroblast growth factor 2 (FGF2) gene (rs11737764), fibroblast growth factor receptor 3 (FGFR3) gene (rs6599400), and one SNP located in p53 binding protein homolog (MDM2) gene (rs1690916) was performed using custom assay based on single-base primer extension with subsequent MALDI-TOF mass-spectrometry measuring.

**Results:** 2 of 6 polymorphisms showed significant association with bone tumor formation: rs1690916 – MDM2 (protective allele A, OR=0.39 [0.19-0.78], p=0.007482) involved in apoptosis, and rs6599400 - FGFR3 (risk allele A, OR=2.15 [1.06-4.34], p=0.03005) involved in proliferation regulation.

**Conclusion:** Significant genetic association of candidate OS-associated SNPs with various types of bone tumors in clinically heterogeneous group may suggest a possible common mechanism of their pathogenesis. Thus, our results confirm previous findings concerning association between certain SNPs and OS and open a new perspective in genetic analysis of predisposition to various histological types of bone tumors. Larger studies are required to confirm this hypothesis.

# BIOMOLECULAR APPROACHES FOR INTEGRATION OF EXPRESSION ARRAY (GENES AND MICRORNA): OSTEOSARCOMA CELLS AND CD99 TRANSFECTANTS IN COMPARISON

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Marika Sciandra<sup>1,2</sup>, Andrea Grilli<sup>1,2</sup>, Maria Teresa Marino<sup>1,2</sup>, Maria Cristina Manara<sup>1,2</sup>, Piero Picci<sup>1</sup>, and Katia Scotlandi<sup>1</sup>

<sup>1</sup> Laboratory of Experimental Oncology – <sup>2</sup> CRS Development of Biomolecular Therapies, Orthopaedic Rizzoli Institute, Bologna, Italy

**Introduction and aims:** osteosarcoma (OS) is the most common bone tumor which affects children and young adults. Emerging evidence suggests this neoplasm as a differentiation disease in which genetic and epigenetic abnormalities could interrupt the process that osteoblast precursors face to become mature cells. The CD99 molecule, down-regulated in OS, acts as a tumor suppressor in this tumor and it is expressed in the normal counterpart, in osteoblasts and mesenchymal stem cells. It seems to emerge as a new mediator in osteoblastic differentiation, being able to overcome the impaired osteoblastogenesis that characterizes osteosarcoma cells. In this study we investigate the molecular aspects responsible for CD99-induced phenotype.

**Materials and Methods:** we examined an OS cell line and CD99 stable transfectants in basal conditions and addressed to differentiate into osteoblastic lineage after 7 and 14 days of treatment. Microarray analyses of gene expression (Affymetrix platform) and microRNA profiling (Agilent platform) were performed. The relationship between the two platforms was explored both following correlation studies and using database predictions for miRNA targets.

**Results:** Cells with forced expression of CD99 were found to be characterized by a sustained down-regulation in gene expression. This led us to explore microRNA profiling of these cells, considering their role in the epigenetic regulation of gene expression. We found significant up-regulation of some miRNAs when we directly compared CD99 overexpressing cells and parental cell line in basal (t0) and during osteoblastic differentiation (t7; t14). Since miRNAs are generally associated with gene expression repression, this suggests miRNA as possible mediators of general gene expression silencing that characterizes CD99 overexpressing cells. Among the up-regulated miRNAs, miR-34a, up-regulated at t0 and t7, attracted our attention due to its functional relationship with p53 signalling and cell cycle regulators. qPCR validation confirmed up-regulation of miR34a in cells overexpressing CD99 either in basal and in differentiative conditions. This is in line with a recent report on Ewing sarcoma (Nakatani F. *et al.*, 2012) and with the general oncosuppressor role of this miRNA in cancer. Bioinformatic analysis of the cross-talk between gene expression and miRNA profile of these cell indicated involvement of TGF $\beta$  signalling, with AKT1 and SMAD2 and 4 among the leading modulated targets. Functional studies are on-going.

**Conclusions:** The data obtained in this study support the role of CD99 as a tumor suppressor that mediates mechanisms of transcriptional repression likely associated to changes in miRNA expression. Up-regulation of miR34a as well as regulation of TGF $\beta$  signalling appears to be crucial mediators that deserve further investigation.

# INDICATION FOR RADIO THERAPY AFTER RESECTION OF PIGMENTET VILLONODULAR SYNOVITIS

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Schauwecker, J.<sup>1</sup>; Horn, C.<sup>2</sup>, Rudert, M.<sup>2</sup>, von Eisenhart-Rothe, R.<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Klinikum rechts der Isar, Technical University of Munich, Germany

<sup>2</sup>Department of Orthopedic Surgery, Koenig-Ludwig-Haus, University of Wuerzburg, Germany

**Objectives:** Pigmented villonodular synovitis (PVNS) also called tenosynovial giant cell tumor is a rare tumor-like lesion causing local destruction of the joint. Along with its semimalignant histology tumor recurrence is the main complication after resection. Thus the following retrospective study should clarify the adequate surgical method and the indication for additional irradiation therapy depending on surgical method and type of PVNS.

**Materials and Methods:** Between 1997 and 2007 43 patients underwent surgery for PVNS of the hip (6), the knee (33), and ankle (3). 24 patients were showing a diffuse type, 19 a localized type of PVN'S. 39 patients following arthroscopical (7) or open (32) treatment were included in a retrospective study with a mean follow-up of 37.2 months. Tumor recurrence according type of PVNS and surgical method have been analyzed statistically.

**Results:** 6 patients (86%) following arthroscopical treatment showed recurrence of PVNS after 36.3 (5.9-66.6) months. 8 (25%) patients following open surgical treatment showed recurrence of PVNS after 85.1 (69.2-101) months. Thereby 12 patients (50%) with diffuse type developed recurrence after 63.6 (44.2-83) months and 2 patients (13%) with localized type after 103.5 (73.5-133.3) months. Arthroscopical treatment of diffuse PVNS was always (100%) leading to recurrence whereas open surgical treatment showed a recurrence rate of 36.8%.

**Conclusions:** The present study demonstrates that arthroscopical treatment of PVNS is a possible surgical method only in case of localized type and should be avoided in diffuse type. In summary we suggest, that additional radiotherapy should be performed after first recurrence of diffuse type PVNS. After first resection of diffuse type PVNS radiotherapy might reduce tumor recurrence and should be discussed with the patient.

**Keywords:** Pigmented Villonodular Synovitis, Tenosynovial Giant Cell Tumor, Radiotherapy, Recurrence

# THE ADVANTAGES AND DISADVANTAGES OF RADIOTHERAPY AFTER ENDOPROSTHETIC REPLACEMENT FOR EWING SARCOMA.

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M Boffano, C Gaston, R Grimer, S Carter, R Tillman, A Abudu, L Jeys

Royal Orthopaedic Hospital, Birmingham (UK).

**Objectives:** Endoprosthetic replacements are commonly used following resection of Ewing sarcoma in the limbs. If there is either a poor response to chemotherapy or a positive margin, radiotherapy (RT) is usually recommended. We have investigated the oncological and prosthetic outcomes for patients to see what the advantages and disadvantages of radiotherapy have been in this group of patients.

**Methods:** Retrospective review of prospective database.

**Results:** 187 patients have had an endoprostheses for Ewing sarcoma with an age range from 2 to 67yrs. There were 57 proximal femur replacements, 35 proximal tibia, 25 proximal humerus, 24 distal femur and 6 total femur. 49 were extendible replacements in children. 136 patients had wide margins with 51 having marginal or intralesional margins. 104 had >90% necrosis and 83 had <90% necrosis. According to current protocols 82 patients would not have needed RT (ie good margin and >90% necrosis) but 105 should have had RT – although in fact only 38 did have RT.

The local recurrence (LR) rate for the 'good' group was 6% but was 10% for the 'bad' group who did have RT and 15% for the 'bad' group who did not have RT. Overall survival was predicted by chemotherapy response, not by the use of RT. In the patients who had RT the infection rate of the prostheses was 26%, compared to 13% in those who did not have RT. The infection rate was doubled in children with growing prostheses so that a child with a growing prosthesis and radiotherapy had a 44% chance of getting it infected compared to a 11% risk for an adult not having radiotherapy.

**Conclusions:** Although radiotherapy decreases the risk of local recurrence it doubles the risk of infection around a prosthesis. Patients need carefully informing of the risks and benefits of RT around EPRs.

Ivone Ribeiro<sup>1</sup>, Joana Gonçalves<sup>1</sup>, Margarida Caldas<sup>2</sup>, Flávio Videira<sup>3</sup>, Augusto Moreira<sup>3</sup>, Marta Soares<sup>4</sup>, Mariana Afonso<sup>2</sup>, Jorge Guimarães<sup>3</sup>, Sofia Conde<sup>1</sup>

Radiotherapy<sup>1</sup>, Pathology<sup>2</sup>, Surgery<sup>3</sup> and Medical Oncology<sup>4</sup> Departments, Portuguese Oncology Institute -Oporto, Portugal.

**Introduction:** Surgery and adjuvant radiotherapy have been the standard treatment for most deep-seated sarcomas. The subgroup of myxoid liposarcoma (MLS), the second most common type of liposarcoma, has been reported to be more radiosensitive compared with other soft tissue sarcomas. Thus, radiotherapy may be used in neoadjuvant setting, to induce downsizing and promote resectability.

**Objective:** To demonstrate the clinical and histologic response of three patients with MLS to neoadjuvant radiotherapy.

**Material and Methods:** We have retrospectively analyzed three patients diagnosed as MLS in biopsies and were submitted to neoadjuvant radiotherapy. We have analyzed clinical, radiologic and pathologic responses as well as acute toxicity to neoadjuvant radiotherapy.

**Results:** Neoadjuvant radiotherapy has been well tolerated. All patients had a good clinical response with some reduction of tumor volume. Pre-operative Magnetic Resonance Image (MRI) also showed some degree of tumor volume reduction, however without any imagiologic morphologic change compare with initial images. Histologic examination revealed an almost complete pathologic response in all cases.

**Conclusion:** These three cases suport the idea that MLS tumors show significant response to the treatment with neoadjuvant radiotherapy, with a near-complete pathologic response, despite the absence of an accurate correlation with pre-operative imaging studies.

Vasileios Kontogeorgakos<sup>1</sup>, Maria Aggeliki Kalogeridi<sup>2</sup>, Ioannis Gioulbasanis<sup>3</sup>, Ioannou Maria<sup>4</sup>

1. Department of Orthopaedic Surgery, University Hospital of Thessalia, Larissa, Greece
2. Department of Radiation Oncology, University Hospital of Thessalia, Larissa, Greece
3. Medical Oncology Department, University Hospital of Thessalia, Larissa, Greece
4. Pathology Department, University of Thessalia, Larissa, Greece

**Introduction:** Radiation recall phenomenon is an inflammatory reaction appearing to previously irradiated areas. Anticancer agents including doxorubicin, taxanes and antimetabolites such as gemcitabine have been reported to trigger this phenomenon when administered after radiation therapy. The frequency of this poorly understood phenomenon may have been underestimated in the past. Timely diagnosis is of paramount importance for the appropriate management of associated symptoms.

**Material - Aim:** We present a case of a 56 year-old man with a poorly differentiated, non- small cell cancer of the right upper lung lobe originally presented with stage cT<sub>3</sub>N<sub>2</sub>M<sub>x</sub> (IIIb). The patient was referred for definite chemoradiotherapy. He received the first chemotherapy cycle with the combination of Cisplatin 75mg/m<sup>2</sup> (D<sub>1</sub>)<sup>2</sup> and Gemcitabine on 1000mg/m<sup>2</sup> (D<sub>1,8</sub>) and then he was planned for concomitant chemoradiotherapy with 33 daily fractions to a total dose of 66Gy concurrently with weekly Cisplatin (40mg/m<sup>2</sup>). Finally, he was planned to receive 5 additional cycles of Cisplatin - Gemcitabine. During the fourth cycle of his post-radiation chemotherapy the patient complained about a newly presented pain of his right shoulder. The pain became constant and severe within a week, aggravated by shoulder motion. During physical examination a very painful nodule was palpated in the subscapularis muscle. No skin reaction was present. MRI of the shoulder revealed a fusiform swelling of subscapularis muscle, within the radiotherapy portal. He was offered a diagnostic biopsy and histology revealed inflammatory cells within the muscle.

**Results:** The diagnosis of myositis as a radiation recall phenomenon was first in line. Treatment consisted of steroid im to the involved muscle and per-os therapy. Immediate relief of pain was noticed. This report joins a small number or radiation recall events related to Gemcitabine exposure. However, radiation myositis in the absence of cutaneous involvement, as in this case, has rarely been described in the literature.

**Conclusion:** Myositis should be kept in mind as a radiation recall phenomenon whenever a patient presents with pain within a previous irradiation field during exposure to certain chemotherapeutic regimens.



## POST RADIATION SARCOMA: A SINGLE INSTITUTION EXPERIENCE ON 52 CASES

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Elisa Pala, MD; Giuseppe Bianchi, MD; Andreas F. Mavrogenis, MD; Carlo Romagnoli, MD; Giovanni Guerra, MD; Pietro Ruggieri, MD, PhD;

IV Department of Orthopaedics, University of Bologna, Istituto Ortopedico Rizzoli, Bologna, Italy

**Objectives:** Radio induced sarcomas are rare. We report our experience about incidence, treatment and outcome of fifty-two patients followed at long term. We retrospectively reviewed our experience to characterize prevalence, treatment, relapse and survivorship at long term follow up of this rare disease.

**Material and Methods:** Fifty-two patients aged from 14 to 83 years (mean 49 years), were treated from 1980 to 2008. Lesions affected the femur (16), pelvis (11), tibia (6), clavicle (6), scapula (4), spine (3), humerus (3), skull (2) and sacrum (1). The mean radiation exposure dose for the patient was 33 Gy (range from 25 to 50 Gy) with a mean interval from radiation of 15.1 years (range 5-30 years). Forty-five patients had post-radiation bone sarcoma, seven had post-radiation soft-tissue sarcoma. There were thirty-five secondary osteosarcomas, sixteen secondary high grade spindle cell sarcomas and one case of secondary angiosarcoma. Limb salvage surgery was performed in 24 cases, amputation in 15 cases. Thirty-two patients were treated with neoadjuvant chemotherapy according to different protocols, twelve patients had surgery as first treatment, one patient underwent embolization, five had chemotherapy only, two patients received palliative care. Statistical analysis with Kaplan Meier curves and Cox regression multivariate analysis were performed.

**Results:** At a mean follow up of 4 years twenty-one patients were disease-free, seven were alive with disease, twenty-four died with disease, six local recurrences were observed and 12 patients developed lung metastases. Kaplan Meier curves showed an overall survival of 53%, 47% and 42% respectively at 2, 5, 5 and 10 years. Prognostic influence of margins, neoadjuvant chemotherapy and site of tumor was evaluated at multivariate statistical analysis: patients with wide surgical margins and neoadjuvant chemotherapy, with tumor in clavicle and in the tibia had better survivorship, without statistical significance. Metastatic disease at diagnosis influenced survivorship, without statistical significance.

**Conclusion:** Post radiation sarcoma has always had a poor prognosis, in previously reported literature. Prognosis improved with recent treatments, as from our analysis. A high percentage of patients can be treated with neoadjuvant chemotherapy and surgery. In most patients, limb sparing surgery is possible and safe, but the expectation of life is poor.

## ORGAN AND GROWTH PRESERVATION WITH PERIOPERATIVE HIGH DOSE-RATE BRACHYTHERAPY (PHDRB) AND LIMITED-DOSE EXTERNAL IRRADIATION (EBRT) IN NON-RHABDOMYOSARCOMA PEDIATRIC SOFT TISSUE SARCOMAS (PSTS).

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<sup>1</sup>San-Julián M; <sup>1</sup>Vázquez-García BL, <sup>2</sup>San-Miguel I; <sup>2</sup>Rodríguez-Ruiz M; <sup>2</sup>Olarte A; <sup>3</sup>Sierrasesúmaga L; <sup>2</sup>Martínez-Monge R

<sup>1</sup>Department of Orthopaedic Surgery, <sup>2</sup> Department of Radiation Therapy, <sup>3</sup> Department of Paediatrics. University of Navarra – Pamplona - Spain

**OBJECTIVE:** To decrease radiation-related long-term toxicity in patients with pSTS.

**PATIENTS AND METHODS:** Eight patients (two girl, six boys) with a median age of 11 years (range 7 - 15 years) were treated between 2001 and 2010 with conservative surgical resection and PHDRB (24Gy in 6 b.i.d. treatments) followed by 27Gy of EBRT three weeks later. Site-appropriate chemotherapy started at the commencement of EBRT.

**RESULTS:** After a median follow-up of 5 years (range, 1–8), only two patients had grade 1 or greater side effects (grade 2 fibrosis in a forearm pSTS and grade 2-3 cosmesis/atrophy in a perimandibular sarcoma). Two patients with metastatic disease at diagnosis died of disease without evidence of locoregional failure at 1 and 1.3 years, respectively. The remaining 6 patients are alive and without evidence of disease.

**CONCLUSION:** PHDRB of 24Gy combined with 27Gy of EBRT is highly efficacious in pSTS and preserves organ function and cosmesis in the majority of the patients. Further refinement is needed to minimize long-term morbidity.

# ROLE OF RADIO THERAPY IN TREATMENT OF ADULT-TYPE NONRHABDOMYOSARCOMA IN CHILDREN - SINGLE CENTER EXPERIENCE

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J. Bokun<sup>1</sup>, Paripović L<sup>1</sup>, V. Ilić<sup>1</sup>, J. Sopta<sup>2</sup>, Z. Vučinić<sup>3</sup>, N. Lujic<sup>3</sup>, Z. Bekić<sup>1</sup>, M. Nikitović<sup>1</sup>

<sup>1</sup> Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

<sup>2</sup> Institute of Pathology, School of Medicine, Belgrade, Serbia

<sup>3</sup> Institute for Orthopedic surgery "Banjica", Belgrade, Serbia

**Introduction:** The aim of our study was to analyze the results of multimodal therapy and the role of radiotherapy in children and adolescents with adult type nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) treated at the Institute for Oncology and Radiology of Serbia.

**Materials and methods:** Between 1996 and 2010, 17 children (11 male, 6 female) with adult type of NRSTS were treated. Median age at diagnosis was 12 years (range 3 to 18 yrs.). There was 7/17 (41.1%) patients with malignant peripheral nerve sheath tumour (MPNST), 2 patients with clear cell sarcoma, 2 with alveolar soft part sarcoma, 1 with epithelioid sarcoma, 1 neuroepithelioma, 1 liposarcoma, 1 leiomyosarcoma, 1 fibrosarcoma and 1 mesenchymal chondrosarcoma.

Primary site of tumor was extremities in 9, trunk and thorax in 1, head and neck in 3 and pelvis in 4 cases. Most of them (12 pts.) had large tumor (> 5 cm). There was 2/17 (11.76%) pts with metastatic disease, 1 with pulmonary metastases and 1 with lymph node involvement. They were treated using multimodality therapeutic approach including surgery, chemotherapy and radiotherapy.

**Results:** Grossly complete tumor resection had 8 pts. and they were classified as IRS group I. 4 pts. classified as IRS II, 1 pt. IRS III and 2 pts as IRS IV. Chemotherapy was administered in 16/17 pts. neoadjuvant chemotherapy in 8 pts. The chemotherapy regimens were VACA, EVAIA and CEVAIE. Radiotherapy (RT) was performed in 12 pts. In 10 patients RT was postoperative, concomitantly with chemotherapy. The total dose ranged from 4400 to 6000 cGy, in conventional fractionation. Daily fractionation from 170- 200 cGy. Palliative irradiation was performed for 2 pts.

During the 15 to 175 months follow-up period (Me= 65 months), overall survival rate was 73,9 % and disease free survival rate was 68,1 %.

**Conclusion:** Complete surgical excision is the mainstay of therapy. Postoperative radiotherapy is acceptable for localized NRSTS with gross residual disease or microscopic residual tumor. Combination of limited surgery and RT should be able to achieve local control with superior functional result. Preoperative RT is area of further investigation.

Masanari Aono, Tomoaki Suzuka, Takaaki Kuroda, Masahiro Yoneda, Minoru Kato, Akira Matsumura, Sadahiko Konishi, Kenichi Kazuki

Department of Orthopaedic Surgery, Osaka City General Hospital, 2-13-22, Miyakojimahondori, Miyakojima-ku, Osaka 534-0021, Japan - TEL:81-6-6929-1221 FAX:81-6929-1091

**Background:** With advances in the treatment of lung cancer, the prognosis of patients with bone metastases from lung cancer has been improving. We attempted to evaluate the clinical outcomes and prognosis of patients with bone metastases from lung cancer.

**Patients and methods:** We retrospectively investigated the charts of 35 patients diagnosed with bone metastases from non-small cell lung cancer (NSCLC), who visited and consulted the Department of Orthopaedic Surgery at Osaka City General Hospital between January 2007 and April 2011. There were 18 men and 17 women, and the mean age at the time of first visit to our department was 64 years. We assessed their clinical outcomes by using the following parameters: the location of bone metastases; skeletal-related events (SREs); treatment of SREs, including bisphosphonates (BPs); epidermal growth factor receptor (EGFR) mutation; treatment of lung cancer with conventional cytotoxic chemotherapy and molecular target-based therapy; and prognosis.

**Results:** Among all 35 patients, there were pathological fractures in 9 cases (surgical indication in 7 cases), and bone biopsy was performed in 15 cases. Radiotherapy was performed in 24 cases. EGFR mutation was determined in 12 cases, and EGFR-targeted therapy was performed in 14 cases and cytotoxic chemotherapy in 20 cases. BP treatment was performed in 23 cases. In the follow-up period (mean, 197 days), 16 patients died of disease, 13 patients were alive with disease, and 6 patients were lost to follow-up. The median survival time was 357 days.

**Conclusion:** SREs cause significant loss of activity of daily living and quality of life in NSCLC patients. It is important that orthopedic surgeons in cancer hospitals diagnose bone metastases from NSCLC smoothly and indicate suitable treatment to prevent SREs. As a consequence, these patients can be treated with chemotherapy for NSCLC, including EGFR-targeted therapy, according to the routine protocol. Such therapeutic strategy may synthetically improve the prognosis of NSCLC patients with bone metastases.

## PROGNOSTIC FACTORS FOR PATIENTS WITH SOLITARY BONE METASTASIS

023

Manabu Hoshi, Jun Takada, Naoto Oebisu, Makoto Ieguchi, Shinji Takahashi, Masanari Aono, Masatsugu Takami, Hiroaki Nakamura

Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.

**Objective:** The term “solitary bone metastasis” is defined in the present study as a single bone metastasis originating from a primary cancer without visceral organ metastasis. We assessed the survival rates and prognostic factors in 42 patients with solitary bone metastasis, and discussed the impact of different surgical strategies on survival.

**Materials and Methods:** We retrospectively analyzed data from 42 patients who underwent treatment for solitary bone metastasis at a single institution. There were 25 men and 17 women. The median age of the patients was 64.5 years (range 41–82 years). The patients were followed for an average period of 21.2 months (range 0.4–127.3 months). Their clinical records were retrospectively reviewed. Factors influencing survival were determined using univariate and multivariate analyses. Particular attention was paid to the orthopedic surgery used for solitary bone metastasis.

**Results:** The one-year survival rate was 76.5%, and the median survival period was 30.0 months. The presence of primary cancer and poor performance status were identified as independent prognostic factors using Cox regression multivariate analysis. Tumor resection and surgical margin were not significantly related to patient survival.

**Conclusions:** The results of this analysis indicated that the prognosis for patients with solitary bone metastasis depended on the presence of primary cancer and on poor performance status.

# PERIOPERATIVE MORTALITY FOLLOWING ABOVE-KNEE AMPUTATIONS INDICATED FOR BONE AND SOFT TISSUE TUMOURS.

028

*P Brewer, BSc, MBChB, FY2 Doctor*

*Z Riddell, BSc, Medical student*

*RJ Grimer, FRCS, Consultant Orthopaedic Surgeon*

*L Jeys FRCS, Consultant Orthopaedic Surgeon*

*The Royal Orthopaedic Hospital Oncology Service,  
Bristol Road South, - Birmingham, - B31 2AP.*

Whilst there are numerous studies investigation perioperative mortality of amputations performed for peripheral vascular disease, there are few studies exploring this in oncology patients. The authors have reviewed their experience in oncology patients who had had an above-knee amputation (AKA), investigating the incidence of reported thromboembolic events, and death.

**Method:** Retrospective review of data stored on a prospective database.

**Results:** 484 patients were identified that had had an above-knee amputation between 1980 and 2011. The most common diagnosis leading to amputation was osteosarcoma (45%) followed by chondrosarcoma (6%). The majority of patients (301) underwent their above knee amputation as a primary procedure (62%). There were two inpatient deaths soon after the above knee amputation (mortality 0.4%) and a further two deaths within 30 days of the procedure (30 day mortality 1%). Only two deaths were directly related to the procedure and were due to a pulmonary embolism. The incidence of nonfatal, clinically evident thromboembolic events was 0.6% in the defined perioperative period of 30 days. The one year survival was 79% and the five year survival was 52%. Patients who had an amputation due to failure of reconstruction were found to have a better survival.

**Conclusion:** Above knee amputations are performed mainly for vascular indications but also for bone of soft tissue tumours of the lower limbs; representing two completely different patient groups reflected by the perioperative risk, significantly lower in oncology patients (<1% vs 8 to 23%). Although a high risk group there is no consensus regarding thromboprophylaxis due to the increased risk of bleeding. However, due to the low complication rates of modern methods of prophylaxis the authors propose routine prophylaxis for patients undergoing above knee amputations.

## SERUM METAL ION LEVELS IN PEDIATRIC PATIENTS FOLLOWING KNEE RECONSTRUCTION USING MEGAPROSTHESES

029

J. Friesenbichler<sup>1</sup>, W. Maurer-Ertl<sup>1</sup>, J. Szkandera<sup>2</sup>, P. Sadoghi<sup>1</sup>, C. Weger<sup>1</sup>, U. Pirker-Frühauf<sup>1</sup>, A. Leithner<sup>1</sup>.

<sup>1</sup>Department of Orthopaedic Surgery, Medical University of Graz, Austria.

<sup>2</sup>Department of Oncology, University Clinic of Internal Medicine, Medical University of Graz, Austria.

**Purpose:** The effects of systemic metal ion exposure in patients with implants made of common prosthetic alloys are still a matter of concern. The aim of the study was to determine the measurement values of cobalt (Co), chromium (Cr) and molybdenum (Mo) in the serum of paediatrics and young adults following tumour resection and reconstruction of the knee using fixed hinge megaprotheses as well as the functional outcome.

**Methods:** Blood was taken from 10 patients [mean follow-up: 109 months (range, 67 to 163)] treated with fixed hinge megaprotheses (HMRS, Stryker, Mahwah, NJ) and analysis was carried out using electrothermal graphite furnace atomic absorption spectrometry (ET-ASS). For functional evaluation the MSTS Score, WOMAC Score and KSS were used.

**Results:** After an average follow-up of 109 months the mean results for cobalt were 5,07 µg/L (range, 0,40-12,80 µg/L), for chromium 4,20 µg/L (range, 1,48-8,91 µg/L) and for molybdenum 0,55 µg/L (range, 0,10-0,90 µg/L). The values for Co (normal: 0-0,50 µg/L) and Cr (normal: 0-1,90 µg/L) were tenfold and twofold, respectively, increased, while Mo (normal: 0-1,0 µg/L) was within the limits. Overall, the functional outcome was good to excellent in all patients (means: MSTS: 28 pts (range, 22-30), WOMAC: 3 (range, 0-9), KSS Part 1: 92 (range, 80-100), KSS Part 2: 97 (range, 80-100).

**Conclusion:** Determining the concentrations of metal ions following fixed hinge total knee arthroplasty revealed significant increments for Co and Cr. The authors believe there might be an additional metal ion release from the surface of the prosthesis although the metal-on-polyethylene articulation. Nevertheless, long-term studies are required to determine adverse effects of Co, Cr and Mo following total hip replacement as well as total knee arthroplasty.



# CAN WE USE THE TORONTO EXTREMITY SALVAGE SCORE TO MEASURE FUNCTIONAL OUTCOME IN PAEDIATRIC DESMOID FIBROMATOSIS?

032

G. Erturan<sup>1\*</sup> (Corresponding author), H. Holme<sup>2</sup>, A. Cassoni<sup>2</sup>, R. Tirabosco<sup>3</sup>, R. Pollock<sup>4</sup>, T. Briggs<sup>4</sup>, M. Michelagnoli<sup>2</sup>

<sup>1</sup> Oxford Trauma Unit, John Radcliffe Hospital, Headley Way, Headington, Oxford, Oxfordshire, OX3 9DU. UK.

<sup>2</sup> The London Sarcoma Service, University College London Hospital, 235 Euston Road, London. NW1 2BU. UK.

<sup>3</sup> Department of Pathology, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP. UK.

<sup>4</sup> The London Sarcoma Service, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP. UK.

**Introduction:** Desmoid fibromatosis (DF) is a heterogeneous condition with lack of consensus regarding therapy. Fatality is rare but repeated surgery prevalent. Functional assessment for this group is not well established, although we believe it to be an important marker of treatment success. No validated self-assessment score exists for non-malignant limb tumours and this may explain why no previous reports exist in the literature. However, we elected to use the Toronto Extremity Salvage Score (TESS) developed and validated by Davis *et al.* for self-assessment of problems with daily life after treatment of limb sarcoma. The TESS is a percentage score based on 30 questions to evaluate disability, psychosocial factors, and their relationship to physical disability that has shown reliability, validity, and responsiveness for patients with an extremity tumour.

**Objectives:** The London Sarcoma Service, one of the largest centres in Europe, set out to retrospectively review self-assessed functional outcome using the TESS.

**Methods:** All young people (< 21 years), with a histological diagnosis of DF in an extremity, from 2003 to 2010 were included. Nineteen children were assessed by telephone or post using the TESS questionnaire.

**Results:** Median time from diagnosis to TESS was 97 months and was not correlated with score. TESS was lower in children who underwent surgical resection compared with those who did not, although this was not significantly significant ( $p=0.12$ ). Five children had non-surgical therapy involving chemotherapy in 3 children, 1 child had diclofenac alone, and a further is still under observation, with a median TESS of 75.5%. Median TESS of those children receiving cytotoxic and non-cytotoxic therapies was high (median TESS 75.5%), despite a trend towards advanced inoperable disease. TESS was lower in those receiving radiotherapy (median 52.5%). It happens that the TESS analysis in this cohort took place greater than 2 years from treatment in all children except one at 15 months. We found children with progressive disease, 5 or more treatment modalities, or greater than 6 events had lowest outcome scores.

**Conclusions:** These finding correlates with clinical experience, confirming that progressive disease or multiple treatment modalities impart a functional disadvantage. Additionally, while radiotherapy is a useful treatment modality, the consequential functional impairment should not be underestimated and will continue to limit its use in younger patients. Longitudinal data may aid optimisation, validation and development of treatment strategies. We suggest an annual formal objective assessment of function with additional assessment prior to a new therapeutic modality. To facilitate ease of completion, we propose a touch screen electronic tablet interface for patient input of questionnaires while waiting for outpatient clinical review.

## OUTCOME AND PROGNOSTIC FACTORS FOR NON-METASTATIC OSTEOSARCOMA OF THE EXTREMITY: CCHE EXPERIENCE

042

Manal A. Zamzam <sup>(1)</sup>, Emad Ali H. Moussa <sup>(1)</sup>, Ahmed El ghoneimy <sup>(2)</sup>, Mohamed S. Zagloul <sup>(5)</sup>, Hala Taha <sup>(3)</sup>, Magdy El Sherbiny <sup>(2)</sup>, Iman Goda <sup>(3)</sup>, Sameera Ezzat <sup>(4)</sup>, Ranin Magdy <sup>(4)</sup>

(1)Department of Pediatric Hematology/Oncology-The New Children's Cancer Hospital (2)Department of surgical Oncology Oncology-The new children's cancer hospital (3) Department of Pathology-The New Children's Cancer Hospital (4) Department of Research-The New Children's Cancer Hospital (5)Department of Radiation Therapy-The New Children's Cancer Hospital .

**Introduction:** The evaluation of factors affecting systemic and local recurrence and final outcome are extremely important in defining risk-adapted treatments for patients with non-metastatic osteosarcoma of the extremity.

**Patients and Methods:** Fifty seven (57) patients treated at The Children's Cancer Hospital-Egypt between July 2007 and December 2010, with a minimum follow up of 12 months patients were retrospectively evaluated in relation to gender, age, tumor site and size, type of surgery, surgical margins, serum levels of alkaline phosphatase and histologic response to preoperative treatment.

**Results:** With a median follow-up of 23 months, the 3-year event-free survival (EFS) and overall survival rates were 70.5% and 77.8 %, respectively. Upon univariate analysis, EFS was significantly related to the age of patients, serum level of alkaline phosphatase, tumor volume, but not to histologic subtype, or histologic response to preoperative treatment. In Multivariate analysis only gender and serum alkaline phosphatase were statistically significantly correlated to survival. Local and systemic recurrences occurred in 12 patients (21%) (Ten patients developed pulmonary metastasis, one patient had both bone and pulmonary and only one patient had local recurrence). While median time to recurrence was 9.2 months, all patients with recurrences were significantly correlated with histologic response to preoperative treatment, and serum alkaline phosphatase.

**Conclusions:** The 3 years EFS, and Overall survival were 70.5% and 77.8% respectively. Serum alkaline phosphatase and histologic response to chemotherapy, as well as age and gender to a lesser extent, can be considered proper tools for deciding risk-adapted treatments for osteosarcoma patients.

**Key Words:** Osteosarcoma, Prognostic factors, Pathological response, Outcome

E. Robertson , F. Maggiani, F. Pezzella, Ni. Athanasou, M. Gibbons

Nuffield Orthopaedic Centre, Oxford University Hospital NHS Trust

**Introduction:** Primary Lymphoma rarely presents in bone. It commonly presents as a painful soft tissue and bony mass rarely with neurological symptoms. These tumours present incidentally in specialist shoulder and upper limb clinics as a presumed benign condition.

## **Aims:**

- 1.To determine the incidence of primary lymphoma of bone, treatment and survival presenting to the Oxford Sarcoma Service
- 2.To assess the functional outcomes following conventional treatment of this disease

**Methods:** The histopathology database was examined for primary lymphoma of bone in the upper limb between 1994 and 2011. External audit cases were not included in this review. Histology was reviewed and further confirmed independently for the purpose of this study.

Patient records were retrieved and patients were excluded if a prior diagnosis of diffuse or non-primary bone disease was identified.

The surviving patients were contacted by telephone and clinical review asked to complete a functional scoring questionnaires, Oxford Shoulder Score (OSS)(1).

**Results:** Forty two patients were initially identified in the study. Nineteen patients were included in the study. The exclusions were 23; 9 for histological confirmation, 10 soft tissue lymphomas, 2 recurrent lymphoma involving bone, 2 unidentified.

The anatomical site of upper limb disease was scapula (4), clavicle (2), humerus (12) and olecranon (1). Treatment included combined (CHOP, rCHOP, PMitCEVO) chemotherapy and radiotherapy in all cases.

Three patients required surgery for fracture including two hemi-arthroplasty and one cementoplasty.

Of 19, 9 died, 3 are lost to follow up, and 6 alive with no disease.

Of the remaining patients, 4 completed final functional assessment, reporting near-normal function. The OSS score ranged from 42 to 48, indicating little functional impediment.

**Discussion:** Primary lymphoma in the bone is recognised in the shoulder as an incidental finding. The treatment is non-surgical with a good functional outcome expected. Even in the presence of pathological fracture a good functional outcome is to be expected.

1. Dawson J, Fitzpatrick R, Carr A. A self-administered questionnaire for assessment of symptoms and function of the shoulder. J Bone Joint Surg Am. 1998 May;80(5):766-7.

## CLINICAL OUTCOMES AND ORTHOPEDIC SURGERY FOR BONE METASTASES FROM HEPATOCELLULAR CARCINOMA

066

*Jun Takada, Manabu Hoshi, Naoto Oebisu, Masanari Aono, Makoto Ieguchi, Masatsugu Takami, Hiroaki Nakamura*

*Department of Orthopedic Surgery, Graduate School of Medicine, Osaka City University – Osaka - JAPAN*

**Objectives:** There have been few clinical reports concerning bone metastases from hepatocellular carcinoma (HCC). The aim of the present study was to elucidate the clinical outcomes of HCC metastases to bone.

**Material and Methods:** The clinical records of 15 patients diagnosed with HCC metastases to bone were retrospectively reviewed. The patients' mean age was 70.8 years. Clinical features, treatments and outcomes were analyzed.

**Results:** Extrahepatic metastases, except to bone, were detectable in the lymph nodes of three patients (20.0%), the lungs of two patients (13.3%) and the adrenal glands of two patients (13.3%). Radiation therapy was carried out at 31 sites in 13 patients and its efficacy was calculated to be 80.6%. Orthopedic surgery was undertaken at 15 sites in 10 patients. Unexpected mortality due to sudden bleeding occurred in two patients soon after surgery.

**Conclusions:** Radiation therapy may be the first-choice palliative treatment for bone metastases from HCC. If the condition allows for residual liver function and a coagulative pattern, surgery should be considered for the treatment of some severe pain and symptoms. Surgical planning, such as preoperative transarterial embolization or intraoperative cementing, may play an important role in reducing intraoperative bleeding, which can lead to liver failure and death.

Kunze B, Haas HP, Ipach I, Kluba T

Department of Orthopaedics, University of Tuebingen, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany

**Aim:** Due to the heterogeneity of histological subtypes of soft tissue sarcoma as well as the different response to neoadjuvant therapy, uniform conclusions about therapeutic concepts, survival time and the optimal restaging scheme are difficult.

The established follow-up scheme “soft tissue sarcoma” at our institution was reviewed and modified based on the study data.

**Method:** The study included 117 patients (159 operations) with soft tissue sarcoma, which had been treated surgically between 2006 and 2010 at our institution. 7 patients were excluded because of incomplete patient records. In addition to the demographic data, the preoperative and postoperative follow-up imaging studies were analyzed in regard to the sensitivity to detect distant metastases and local recurrence.

**Results:** NOS was the most common histological entity (21.5%). Primary metastases were seen in 17% of the patients (GI 5%, GII 16%, GIII 78%). 67% of primary metastases were seen in the lung and the lymph nodes. Regarding the follow-up examinations, the local MRI (89%) and the CT-chest (40%), had the highest priority for the detection of metastases (60% affecting the lung).

Accordingly to these data a relevant modification of the follow-up scheme was done. Radiographs of the chest and bone scintigraphy directed not significantly to the early diagnosis of metastasis.

Factors for a poor prognosis were primary metastasis, high-grade tumours and several histological entities.

**Conclusion:** The importance of adequate follow-up was shown. To evaluate the individual prognosis, multiple factors have to be considered. The MRI (local recurrence) and CT (pulmonary metastases) are demanded at regular intervals in the follow-up. The grading of the tumour should be considered in the follow-up frequency of the lung examination to avoid unnecessary radiation exposure and costs in patients with low grade tumours.

# THE INFLUENCE OF NO ADJUVANT CHEMOTHERAPY ON THE PATIENTS SURVIVAL WITH OSTEOSARCOMA OF THE LOWER EXTREMITY BONES.

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Mirza A.Gafur-Akhunov, Khurshid G.Abdikarimov, Sundr D.Urunbayev, Djamila Sh.Polatova

National Oncology Research Centre, Tashkent, Uzbekistan

**Aim:** to study the treatment results of patients with osteosarcoma (OS) of lower extremity with applying the different conducting methods of no adjuvant chemotherapy.

**Materials and methods:** Treatment results analysis of 122 patients with OS of lower extremity was performed. Men-80(65, 6%), women-42(34, 4%).Average -19, 8+0, 9. Patients were divided into 3 groups: I group-34 patients (27, 9%), who had been performed no adjuvant systemic chemotherapy +operative intervention (OP). II group-52 patents (42, 6%), who had been performed prolonged intra-arterial regional chemotherapy (PIACT) +OP.III group-36 patients (29, 5%) PIACT on the back ground of modifiers+OP have been performed. Chemotherapy was carried out by scheme of CAP. Local hyperthermia with temporary hyperglycemia have used as modifiers.

**Results:** In the I group in 2 (5,9%) patients absolute effect, in 13(38,2%) partial effect, in 15(44,1%) stabilization of process and in 4(11,8%)patients progressing of tumor process was noted. In the II group the absolute effect in 7(13, 4%); partial in 23(44, 2%); stabilization of process in 18(34, 6%) and in 4(7, 7%) patients progressing of tumor process was marked. In the III group absolute effect was in 7(19, 4%), partial- in 18 (50%), stabilization process-in 9(25%) and in 2(5, 6%) patients progressing of tumor process have been observed.

In the I group relapse of tumor in 8 (23, 5%) patients, in the II group in 9(17, 3%), but in the III group in 5(13, 9%) have been observed. Metastasis was detected: till 9 months in the I group in 29, 4%, in the II group in 13, 5%, in the III 5, 6% patients. In the period of 10-18 months 23,5%,19,2%,16,6% and in the period of 19-36months 11,8 %,7,7%,5,6% cases were detected correspondingly by groups. Three-year survival 35,3%, 48,1%, 72,1%, five-year 23,5%, 38,5%, 55,6% was composed correspondingly.

**Conclusion:** Survival rate of patient is 1, 5 times higher in the group of PIACT with modifiers than in the group with pure PIACT and 2, 4 times higher than in the group of patients treated with traditional systemic chemotherapy.

Tomoki Nakamura, Adesegun Abudu, Hiroaki Murata, Robert Grimer, Simon Carter,

Roger Tillman, Lee Jeys

Institution; Oncology Unit, The Royal Orthopaedic Hospital, Birmingham, United Kingdom

**Introduction:** Soft tissue sarcomas (STS) of the pelvis present one of the most challenging problems in musculoskeletal oncology because of the complex anatomy of the pelvis, late diagnosis and large sizes of the tumors. The aim of this study is to determine the outcome and prognostic factors for survival and local recurrence in patients newly diagnosed with STS involving the pelvic region deemed suitable for curative surgical treatment.

**Patients and Method:** The outcome of 122 consecutive patients with newly diagnosed STS involving the pelvic region with at least 5-year follow-up was studied. The mean age at diagnosis was 53 years. There were 62 male and 60 female patients. The mean follow-up period was 72 months (range, 3-336). The mean tumor size at diagnosis was 11 cm. 63 patients had histologically grade 3 sarcomas, 32 were grade 2 and 27 were grade 1. The primary tumor locations were extra-pelvic (n=98), intra-pelvic (n=11), and combined (n=13).

**Result:** Surgical treatment was excision in 116 patients and hindquarter amputation in 6 patients. Overall survival in 122 patients was 59.8% at 5 years. Local recurrence occurred in 21%. Development of local recurrence was related to surgical margin ( $p=0.01$ ), and tumor location ( $p=0.01$ ). Local recurrence and tumor histological grade influenced development of metastases and overall survival in multivariate analysis ( $p<0.0001$ ,  $p=0.003$ , respectively).

**Conclusion:** Patients who develop local recurrence have a poor prognosis. The Patients with intra-pelvic and combined pelvic STS represent a particular group with very high risk of local recurrence even with radiotherapy.



# AN UNUSUAL LOCALIZATION OF EWING'S SARCOMA: INTRADURAL EXTRAMEDULLARY SPACE. TREATMENT AND OUTCOME

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Ferraresi V.<sup>1</sup>, Zoccali C.<sup>2</sup>, Prencipe U.<sup>2</sup>, Marolda G.<sup>2</sup>, Nuzzo C.<sup>2</sup>, Anelli V.<sup>3</sup>, Salducca N.<sup>2</sup>, , Biagini R.<sup>2</sup>

<sup>1</sup>Division of Medical Oncology A, <sup>2</sup>Division of Orthopedics, , <sup>3</sup>Division of Radiology  
Regina Elena National Cancer Institute  
Rome - ITALY

**Background:** Ewing's sarcoma is one of the most aggressive and recognized primitive malignant bone tumors, nevertheless it is of rare presentation in extraosseous sites. The most frequent sites of extraskeletal Ewing's sarcoma are the chest wall, lower extremities, and the trunk. We report a case of intradural extramedullary Ewing's sarcoma arising in L1-L4 levels and treated with exclusive chemo-radiotherapy.

**Case report:** A 40 year-old female was referred to our department complaining of progressive paralysis in her lower extremities. Due to a radiological diagnosis of suspect ependymoma, the patient had recently undergone a lumbar surgery but the surgeon, after opening the dura mater, and verifying the unusual nature of the mass, performed a biopsy confirming the bony origin of the tumor. The histological examinations revealed a highly cellular poorly differentiated malignant neoplasm composed for the most part of quite uniform rounded cells with limited amounts of amphophilic cytoplasm and relatively bland nuclei with evenly distributed chromatin. Immunostains for keratin, EMA, S-100 protein, synaptophysin, desmin and TLE1 were negative, but there was a diffuse membranous positivity for CD99 and FLI-1 in virtually 100% of the neoplastic cells fitting to the diagnosis of Ewing's intradural sarcoma. Basing on the diagnosis of Ewing's sarcoma, the patient was rapidly addressed to a neoadjuvant chemotherapy with Vincristina, Adriamicina, Ciclofosfamide, Ifosfamide, Dactinomicina and Etoposide. After neoadjuvant treatment the patient had a subtotal recovery of her neurological function with a slight effort deficit, and an almost complete response as documented by total body CT/PET and spine MRI. After multidisciplinary discussion of the case and considering a wide surgery not feasible, it was decided to undergo the patient to a definitive radiotherapy as local treatment followed by adjuvant chemotherapy employing the same agents used in neoadjuvant setting, the patient being evaluated as a "good responder". The adjuvant chemotherapy treatment is still ongoing.

**Conclusion:** being this localization extremely rare, no guidelines are present in literature, but considering the aggressiveness of the tumor and its behavior probably, not being possible to obtain wide margins, chemotherapy ad systemic therapy and radiotherapy for local control should be the best approach. Indeed, even though some author sustains the importance to remove the major part possible of tumoral mass, there is no evidence in literature that intralesional surgery followed by radiotherapy give better results.

Centomo, H. PhD<sup>3</sup>, Barry, J. MSc<sup>1</sup>, St-Yves, H.<sup>3</sup>, Rakovich, G. MD<sup>2</sup>, Isler, M. MD<sup>1</sup>, Turcotte, RE. MD<sup>4</sup> and Mottard, S. MD<sup>1</sup>.

1-Department of Orthopedic Oncology Surgery, Montreal University, Quebec, Canada.

2-Department of Thoracic Surgery, Montreal University, Quebec, Canada.

3-Faculty of medicine, Montreal University, Quebec, Canada.

4-Division of Orthopedic Surgery, McGill University, Quebec, Canada.

**Objectives:** The main objective of this study was to assess the prognostic factors of patients presenting with aggressive sarcomas (bone and soft tissue) with early onset of pulmonary metastasis (< 3 years) . Overall survival was assess according to metastasis treatment.

**Materials and Methods:** Patients from an orthopedic oncology referral center, between 1992 and 2011, that were diagnosed with soft tissue or bone sarcomas and developed lung metastases were retrospectively reviewed. 96 patients were identified out of which 56 patients with complete follow-up were included in the study. Factors affecting overall survival were analyzed, with special interest in metastases treatment. Average follow up was 35.8 ± 26.5 months. Mean age at diagnosis was 48.8 ± 18.7 years.

**Results:** 5 years survival was 14.3%. 75% of sarcomas were situated in lower extremities and 19.6% in upper extremities. 41.1% of patients had metastatic lung disease at initial presentation. The primary neoplasm was mainly soft tissue presentation (67.9% where: 23.7% were synovial sarcoma, 13.2% were liposarcoma, 13.2% were myxofibrosarcoma, 10.5% were leiomyosarcoma, 7.9% were epithelioid sarcoma, 5.3% were malignant fibrous histiocytoma (MFH) and 26.2% were others). Bone sarcoma represent 32.1% where osteosarcoma account for 38.9%, Ewing sarcoma for 11.1%, MFH bone for 11.1%, chondrosarcoma for 5.5% and others for 33.4%. Patients presenting with localized disease develop lung metastasis in a relatively short period of time 9.4 ± 7.3 months after the primary diagnosis. 33.9% of patients underwent surgical removal of thoracic metastasis (surgical alone 17.9% and 16.1% for surgery combined with chemotherapy). Aggressive surgical removal of thoracic metastases (lung resection and/or greater than 10 metastatectomies) had a trend towards longer survival period (mean follow-up 47.5 months vs 25.7 months for chemotherapy only and 24.0 months for palliative chemotherapy).

**Conclusions:** Patients with pulmonary metastases following primary sarcomas have poor overall survival. In this study, pulmonary metastases appear early after primary diagnosis and patients showed a poor prognosis. However, patients treated with surgical removal of pulmonary metastasis have a small improvement in their overall survival, but are unlikely to be cured from their disease. This improvement could justify an aggressive approach in younger patients who can tolerate aggressive surgery. However, impacts on quality of life of these patients remain to be determined.

## TACTICS ANALYSIS OF SURGICAL AND COMBINED TREATMENT AT PATIENTS WITH MULTIPLE MYELOMA AND LYMPHOMA OF SPINE.

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Aliev M.D., Musaev E.R., Sokolovsky A.V., Sergeev P.S., Sokolovsky V.A.

Department of Bone and Soft Tissue Tumors, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation.

**Introduction/Objectives:** The aim of the current study was to determine tactical choice of different variants of surgical and combined treatment at patients with hemoblastosis lesion of spine.

**Methods:** A retrospective analysis was conducted on 60 patients with a diagnosis of multiple myeloma and lymphoma of spine who were underwent with vertebroplasty and surgical treatment between January 2001 and December 2011. In group of patients there were 34 (56,7%) males and 26 (43,3%) female, with a mean age of 56 (22 to 81) years, thus 48 (80%) was younger 65 years. Among the treated patients 46 were with multiple myeloma, 7 with lymphoma and 7 plasmacytoma. During the 10 years period in our clinic were executed 60 various operations to patients with hemoblastosis lesion. The mean duration of follow-up after the operation in group of patients with multiple myeloma, plasmacytoma was 11,2 months (1 to 63) and lymphoma 22,4 months (3 to 96). Neurological status was evaluated using the classification system described by Frankel, which was before the treatment "E" at 44, "D" at 6, "C" at 2, "B" at 1 patients with multiple myeloma, plasmacytoma and "E" at 5, "C" at 1, "B" at 1 patients with lymphoma.

**Results:** Overall surviving since surgery during 3 years was 81,5%, during 5 years 68%. While common free of recurrence surviving during 3 years was 46,9%, during 5 years 32,1%. Progressing of the primary disease is revealed in 67,3 % during 5 years. The average pain score (VAS) decreased significantly from pre- (6,3) to post-treatment (2,3). Based at the data of the present research the was developed a new scale of choice of tactics of surgical treatment patients with multiple myeloma and lymphoma.

**Conclusion:** The tactical choice of treatment depends on disease prevalence and prospective term of life. Vertebroplasty and kyphoplasty is an effective minimally invasive procedure for the stabilization of pathologic fractures and instability of vertebra caused by multiple myeloma and lymphoma leading to statically reduction of pain status.

**Key words:** hemoblastosis lesion of spine, scale of choice.

Castellanos-Toledo A<sup>1</sup>, Rivera-Luna R<sup>2</sup>, Cárdenas-Cardós R<sup>1</sup>, Figueroa-Carbajal JJ<sup>3</sup>, Leal-Cavazos CA<sup>1</sup>

<sup>1</sup>Oncology Department and <sup>2</sup>Division of Pediatric Hem/Oncology, Instituto Nacional de Pediatría, México City, MEXICO. <sup>3</sup>Instituto Mexicano del Seguro Social, Cuernavaca, Morelos, MEXICO.

**Background:** Some others prognostic factors are interrelated with the well-known prognostic factors in high-grade Osteosarcoma (HGO), this can result in poor survival and should be considered for appropriate clinical decision making.

**Aim:** To inform the influence of risk factors on prognosis.

**Patients and Methods:** Retrospective, longitudinal and clinical study was performed from Jan/1991-Dec/1998, 58 patients younger than 18 years with extremity HGO and no prior chemotherapy treatment were included. All received CDDP, DOX, CFA and VP-16. Prognostic-factors and Cox analysis with odds-ratio (OR) and  $p < 0.05$  were calculated. Outcome variables were age, histologic patterns (HP), primary site, tumor size (TS), metastatic disease, soft-tissue involvement (STI), histological response (HR) assessed by Huvos-grades and disease-free survival (DFS).

**Results:** Median age was 12 years (5-18y) with 18 patients (31%) younger than 10 years. Skeletal site (SS) distribution was 59% distal femur, 17% proximal humerus, 14% proximal tibia, 7% fibula and 3% proximal femur. 18 patients (31%) had pulmonary metastases and 3 patients (5%) had multifocal disease at diagnosis. There were 74% osteoblastic tumors, 14% osteoblastic and chondroblastic, and 5% chondroblastic. 15 patients had an amputation procedure and 33 patients undergoing limb salvage of which 5 patients (15%) had eventual local recurrence. The more significant associated prognostic factors (APF) for local recurrence were STI at diagnosis (OR=6), grade-II HR (OR=2.8), grade-III HR (OR=10), TS ( $p=0.0350$ ) and chondroblastic-HP ( $p=0.0089$ ). For amputation procedures were SS ( $p=0.0018$ ) and have microscopic surgical margins (MSM)  $p=0.0075$ . For development of metastatic disease were TS ( $p=0.0008$ ), MSM ( $p=0.000$ ), pulmonary metastases at diagnosis ( $p=0.000$ ), SS ( $p=0.000$ ) and chondroblastic-HP ( $p=0.000$ ). For death by tumor activity was poor in HR ( $p=0.0013$ ) and TS ( $p=0.0278$ ). 5-years DFS without APF was 68% Vs 43% with APF ( $p=0.021$ ).

**Conclusions:** APF play a very important roll in Osteosarcoma prognosis and should be considered for appropriate clinical decisions making.

## PUTTING YOUR BEST FOOT FORWARD! IS FOOT SIZE DIFFERENT AFTER ENDOPROSTHETIC REPLACEMENT IN CHILDREN?

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CL Gaston, B Vazquez, RJ Grimer

Royal Orthopaedic Hospital Birmingham, UK

**Introduction:** Limb salvage surgery with growing endoprostheses has allowed for a near normal body image for long term survivors of bone sarcomas with the achievement of equal leg lengths and normal walking. Knowledge of other possible deformities of the limb will help patients accept them later on. This study aimed to determine whether patients with bone sarcomas treated with a growing prosthesis had any discrepancy in their foot sizes at skeletal maturity.

**Methodology:** From March 2011 – February 2012, foot sizes were measured from 53 patients treated with endoprosthetic replacements for bone sarcomas on routine outpatient follow-up at our hospital. 35 (67%) were extendible prostheses. Weightbearing foot tracings were taken measuring maximum length and width of both extremities for comparison.

**Results:** There was a significant discrepancy in foot size of patients who underwent lengthening with an extendible prosthesis compared to those that did not undergo any type of lengthening. Feet were shorter (7.8mm vs 2.8mm,  $p = 0.02$ ) and narrower (3.4mm vs 0.8mm,  $p = 0.07$ ). Leg lengths at final follow-up were not significantly different between the 2 groups.

**Conclusion:** Majority of children with bone sarcomas treated with a growing endoprosthesis while skeletally immature develop a discrepancy in foot size on reaching adulthood.

CL Gaston, M Boffano, RJ Grimer

Royal Orthopaedic Hospital Birmingham, UK

**Introduction:** Superficial soft tissue sarcomas (SSTS) comprise 11-32% of all soft tissue sarcomas. Treatment is wide local excision with various studies recommending margins ranging from 1cm, 2cm, or 3-5cm. The need for adjuvant radiotherapy is controversial as well. The present study was done to document current surgical practices of different sarcoma centres in treating SSTS.

**Methods:** A questionnaire demonstrating typical cases of SSTS was developed by the senior author and sent to 42 surgeons that treated sarcomas from 34 tertiary referral centres specializing in musculoskeletal tumours in 24 different countries. Responses were tabulated and presented here.

**Results:** 27 surgeons (64%) from 21 centres in 14 countries responded to the questionnaire. The mean number of SSTS treated per centre was 21.3/year. There was little consensus between surgeons with regards to their treatment strategies for both primary and secondary treatment after previous inadvertent surgery for SSTS. Surgeons had varying definitions of adequate margins as evidenced by their different treatment protocols after close surgical margins. For patients previously treated with inadvertent surgery, 50% would routinely give adjuvant radiotherapy. 40% would excise the previous surgical bed with an overlying skin ellipse of 1cm or less on either side of the scar.

**Conclusions:** The lack of consensus among sarcoma surgeons with regards to the treatment of superficial soft tissue sarcomas reflects the scarcity of evidence in medical literature. More clinical studies are needed to answer the simple question of what constitutes an adequate margin for SSTS and the corresponding treatment for an inadequate margin.

# PREVENTION AND TREATMENT OF CATHETER-RELATED INFECTIONS AND CATHETER THROMBOSIS IN CHILDREN WITH TUMORS OF THE MUSCULOSKELETAL SYSTEM

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Maxim Rykov, Yury Buydenok

*Institute of Pediatric Oncology and Haematology N. N. Blokhin Cancer Research Center - Moscow - Russia*

**Objectives:** Current standards of treatment of musculoskeletal tumors in children require numerous courses of chemotherapy (at least 10 per year). This long and important stage of treatment requires adequate vascular access, which should be reliable and comfortable for the patient. The usual approach in establishing long-term venous access in child patients is to install a central venous catheter. However, an external central venous system requires meticulous care, control and maintenance, which cannot be achieved and provided while at home in between courses of chemotherapy. Therefore, a central catheter needs to be inserted prior to almost every course of chemotherapy. This procedure requires repeated anesthesia and may cause a number of serious complications, thus delaying the start of the next course or stage of treatment.

Implantable venous port-system are free from many of the disadvantages which are associated with the use of central venous catheters. In contrast to the external venous systems, port-systems are implanted once for the entire period of treatment, reducing the need for the administration of general anesthesia, required when central catheterization is performed on a child patient. However, proper care and maintenance is essential to the long life and function of venous port systems.

Our goal was to reduce the occurrence of infectious and thrombotic complications in children with central venous systems of long-term use.

**Materials and Methods:** From July 2010 to March 2012 we observed 109 patients with tumors of the musculoskeletal system aged between 6 months to 17 years, for 78 of which implanted venous port systems were used and for 31 of which traditional subclavian catheters were used. We evaluated performance against the following criteria: local manifestations of infection, the development of catheter-related bloodstream infections, and cases of catheter thrombosis. Local infectious were treated with an unguent containing Chloramphenicol, and any suspected systemic infection was addressed with antibiotic therapy. In cases of port thrombosis, we injected the system with a 25,000 IU dose of Urokinase with an exposure of 15 minutes.

**Results:** Of the patients implanted with subcutaneous venous ports, periportal tissue infection was noted in 3 cases (3.8%). No catheter-related bloodstream infections were noted. Port catheter thrombosis was observed in 7 cases (8.9%), which presented as lower infusion rate and difficulties with retrograde blood flow. In patients with a traditional subclavian artery catheter, puncture site infection was noted in 21 cases (67.7%). The development of catheter-related bloodstream infections was noted in 8 cases (25.8%). Catheter thrombosis was observed in 17 cases (54.8%). The treatment of 8 cases (47%) of the 17 occurrences of subclavian catheter thrombosis necessitated replacement, together with the associated need for general anesthesia and the risk of complications. To seal the catheter between courses of treatment, we used heparin or a solution containing cyclotaurolidin (when using which no catheter-related bloodstream infections were noted).

All venous ports worked satisfactorily following implantation. All cases of thrombosis were successfully treated.

**Conclusion:** The use of a cyclotaurolidin solution to close the venous system in the intervals between treatments prevents infection. The treatment of catheter-related infections is better effected by a combination of cyclotaurolidin and urokinase, which provides lysis of the microtrombs serving as a source of bacteria in both the catheter and port chamber. The incidence of catheter thrombosis and catheter-related bloodstream infections is significantly higher in patients with subclavian catheters, the treatment of which often requires replacement of the catheter, which is more traumatic and requires general anesthesia, and disrupts treatment.



# HEIGHT PREDICTION IN CHILDREN TREATED WITH POLYCHEMOTHERAPY FOR OSTEOSARCOMA AND EWING'S SARCOMA - A RETROSPECTIVE ANALYSIS

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Magdalena Gilg<sup>1</sup>, Dimosthenis Andreou<sup>2</sup>, Christine Wibmer<sup>1</sup>, Alexander Avian<sup>3</sup>, Petra Sovinz<sup>4</sup>, Per-Ulf Tunn<sup>2</sup>, Andreas Leithner<sup>1</sup>

<sup>1</sup> Department of Orthopaedics and Orthopaedic Surgery, Medical University of Graz

<sup>2</sup> Department of Orthopaedic Oncology, Sarcoma Center Berlin-Brandenburg

<sup>3</sup> Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz

<sup>4</sup> Division of Pediatric Hemato-Oncology, Medical University of Graz

**Objectives:** Prediction of final height in children treated for bone tumours is needed to determine what kind of prostheses can be implanted. A current method for height prognosis is the multiplier method by Paley. Recent publications suggest inhibiting effects of polychemotherapy on longitudinal growth. The aim of this retrospective study was to investigate if this formula is applicable to children who have received polychemotherapy.

**Patients and Methods:** We retrospectively analysed height records of 33 children, 6 female and 27 male, who had polychemotherapy for osteosarcoma or Ewing's sarcoma in our two centres. Actual adult height (Ha) was compared to the height predicted (Hp) by the multiplier method at the date of initial diagnosis. The height difference (Hdiff) Ha minus Hp was also calculated. The data was analysed with descriptive methods and correlation was tested with Pearson's Coefficient. A p-value of < 0.05 was regarded significant.

**Results:** Within one standard deviation 10 children had a correct and 23 children had a false prognosis of Ha with Paley's formula. The estimated adult height was too high in 25 and too low in 8 children. Median Hdiff was -5.0 cm (range -17 to -0.6 cm) in children whose height was overestimated and 5.4 cm (range 0.5 to 8 cm) in those whose height was underestimated. Overall the Hp was 2.3 cm higher than the Ha (p = .013). The absolute error of prediction ranged from 0.5 to 17.0 cm (median 5.0 cm). We found a positive correlation (r = .799, p<.001) between Hp and Ha and a negative correlation between Hp and Hdiff (r = -.417, p= .016).

**Conclusion:** Due to the high amount of false predictions a reliable prognosis on adult height could not be made with Paley's method in our collective. In this study population tall predicted body heights were overestimated. In our dataset the majority of children reached a lower adult height than predicted. Consequently, Paley's formula may have to be adjusted for patients undergoing polychemotherapy for osteosarcoma and Ewing's sarcoma.

# FEATURES OF THE IMPLANTATION OF VENOUS PORT SYSTEMS FOR CHEMOTHERAPY IN CHILDREN WITH TUMORS OF THE MUSCULOSKELETAL SYSTEM

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Maxim Rykov, Yury Buydenok, Anna Shavrova, Nadeжда Ivanova

*Institute of Pediatric Oncology and Haematology N. N. Blokhin Cancer Research Center  
Moscow - Russia*

**Objectives:** The chemotherapeutical treatment of musculoskeletal tumors in children requires numerous courses of chemotherapy (at least 10 per year). An initial problem to be solved before beginning chemotherapy is therefore providing access into the venous system of the child. This venous access must be reliable and comfortable for the patient, should be established once for the entire period of treatment and should entail minimal risk of infection and thrombosis (of both the catheter and vein). External infusion systems, peripheral catheters, and central catheters, including chronic Broviak type catheters, do not satisfy the aforementioned requirements. The best option is a fully implantable venous port system, which in addition to satisfying all the above criteria can significantly reduce the need for the repeated administration of general anesthesia, required in each and any case where a traditional subclavian catheter is introduced in a child patient.

Our goal was to reduce the number of central venous catheterisations, and accordingly the need for general anesthesia, during the treatment of children with musculoskeletal tumors, and to reduce the number of complications associated with central venous catheterisation. We were also aiming to make the installation of central venous systems in children safer.

**Materials and Methods:** From July 2010 to February 2012 78 children with tumors of the musculoskeletal system (aged 6 months to 17 years) underwent the implantation of subcutaneous venous port-systems in order to receive multiple courses of chemotherapy. All surgeries were performed in an operating theatre with the use of ultrasonic and X-ray scanning equipment. Children aged under 15 years underwent implantation under general anesthesia. With child patients over 15 years old we used local anesthesia with sedation.

**Results:** In light of our experience in the installation of central catheters in children, we punctured the internal v. jugularis only after preliminary ultrasonic marking, in order to reduce the risk of complications (for example haemo- and/or pneumo- thorax, and/or trauma to surrounding anatomical structures). We succeeded in puncturing a vein on our first attempt in 74 cases (94,8 %), and on the second attempt in 4 cases (5,4 %). In some complex cases (where the vein was thin or flexible), vein puncture was performed directly under sterile ultrasound navigation. In only 3 cases (3,8 %) was there an accidental puncture of the adjacent carotid artery. Neither haemo- nor pneumo- thorax nor lung injury was detected. After the jugular vein was punctured by the Seldinger method, a wire was introduced under X-ray control using a C-arm. In 59 cases (75,6 %) the wire immediately moved towards the heart in the superior vena cava. In 19 cases (24,3 %) there were problems with the introduction of the wire, whereby the wire folded or moved in other directions, most often in the distal portion of the jugular vein. In 4 cases (5,1 %) the migration of the wire in the opposite subclavian vein was observed, in 9 cases (11,5 %) it migrated in the subclavian vein on the side of the catheterization. In all cases we managed to position the wire properly by using the introducer to introduce the catheter into the superior vena cava, where rapid blood flow and the large diameter of the vessel provides for the effective mixing of chemotherapeutic agents with the blood, and minimizes the risk of developing thrombophlebitis. Since implantation, all venous port-systems have worked satisfactorily, providing for a volume infusion of more than 5 liters per day.

**Conclusion:** The introduction of implantable venous port-systems for the treatment of child patients with tumors of the musculoskeletal system has significantly reduced the number of administrations of general anesthesia, improved the quality of life of the patients and minimized the risk of developing complications during the actual catheterization procedure or during subsequent use of the port-systems. The use of ultrasonic marking (both prior to the puncture of the internal jugular vein as well as during the puncture) permits the avoidance of injury to the adjacent anatomical structures (haemo- and/or pneumo- thorax) and the reduction of the duration of the implantation surgery. The use of an X-ray scanner during the positioning of the port catheter prevents its migration into the veins of the neck and upper extremities, which otherwise happens fairly frequently due to the anatomical peculiarities of children. It is particularly important precisely to place the distal end of the catheter into the superior vena cava above the entrance to the right atrium, since it is exceptionally difficult to adjust the implanted system after the surgery is over.

# CAN THE STUDY OF BODY SCHEMA INFLUENCE THE REHABILITATION PROTOCOL AND THE FUNCTIONAL OUTCOME IN AMPUTEES? PRELIMINARY RESULTS

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Boffano M<sup>1</sup>, Giordano A<sup>2</sup>, Cicolin A<sup>2</sup>, Francese V<sup>2</sup>, Boux E<sup>1</sup>, Piana R<sup>1</sup>.

<sup>1</sup>S.C. Oncologic and Reconstructive Orthopaedics Department – AO CTO/Maria Adelaide Torino - Italy

<sup>2</sup>Sleep Medicine Centre - Neuroscience Department – University of Torino Torino - Italy

**Objectives:** The aim of the study is to assess the self body perception, during wake and sleep, in patients affected by bone and soft tissue sarcomas who underwent amputation to evaluate phantom limb and telescoping and to optimize the therapeutic protocol and the compliance in prosthesis use.

**Materials and Methods:** Nineteen consecutive outpatients referred to S.C. Oncologic and Reconstructive Orthopaedics Department AO CTO/Maria Adelaide Torino (Italy) were evaluated with the collaboration of the Sleep Medicine Centre – Neuroscience Department – University of Torino. Inclusion criteria: diagnosis of bone or soft tissue sarcoma, minimum age 16 years old. Exclusion criteria: impaired cognitive ability, psychiatric disease, ray amputations (or smaller), previous amputation. Patients were divided in two groups: 1-perspective group, patients evaluated within two weeks and 4 months from surgery, and 2-retrospective group, less than 1 year from surgery. The local ethical committee approved the protocol and all patients signed the informed consent form. Patients were assessed using questionnaires and dream content diaries: Kooijman's phantom limb questionnaire [1], a weekly dream content diary, the West Haven-Yale Multidimensional Pain Inventory [2], the Body Image Concern Inventory [3], a clinical assessment of the body image. Statistical analysis was performed by SPSS 17.0 (mean+/-SD, p<0,05).

**Results:** Ten patients fulfilled the criteria for the inclusion in the group 1 and nine patients for the group 2. Nine patients completed the protocol (7 of the perspective group and 2 of the retrospective group). Three of the nineteen eligible patients did not complete the study due to death (1 case) and incomplete protocol compliance.

A preliminary result analysis shows:

- phantom limb can be found in 100% of patients, mainly represented by somato-sensory and movement perceptions; phantom limb pain is referred only by 40% of patients
- telescoping is present in 1/5 of patients, mainly in young people
- all patients with telescoping do not use the prosthesis and refer pain
- all patients with telescoping dream about limb (mainly without limb)
- the prosthesis use seems to be related with the body image concern of patient

**Conclusions:** Although there has been much progress in the surgical treatment of bone and soft tissue sarcomas, amputation is unfortunately still needed in 5-10% of cases [4]. Few studies have evaluated the integration among these phenomena also related to the change of body schema in the dream content. The self-concept schema is influenced by the cognitive generalization about oneself derived from past experiences in a social context [5]. Information about body schema is differently interpreted by each individual also related to a potentially worry-some physical appearance [3] that can lead to cognitive distortions such as phantom limb [6] (70-100% of patients who underwent amputation), phantom limb pain (from 60 to 85%) and telescoping, a phenomenon characterized by the gradual proximal migration of the phantom limb affecting one third of the amputees/patient [7]. When compared with literature data, our results show a lower percentage of phantom limb pain and telescoping, and a significant relationship between telescoping and the use of prosthesis, pain and body image in dreams. If confirmed, these data could help to improve the rehabilitation protocols optimizing the timing of prosthesization with reference to the adaptation of the body schema.

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# NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMA IN CHILDREN- THE CHOICE OF OPTIMAL THERAPEUTIC APPROACH

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Paripović L<sup>1</sup>, Bekić Z<sup>1</sup>, Ilić V<sup>1</sup>, Pudrlja-Slović M<sup>1</sup>, Gavrilović D<sup>2</sup>, Vučinić Z<sup>3</sup>, Sopta J<sup>4</sup>, Bokun J<sup>1</sup>

<sup>1</sup> Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

<sup>2</sup> Institute for Oncology and Radiology of Serbia-Data center Belgrade, Serbia

<sup>3</sup> Institute for Orthopedic surgery "Banjica", Belgrade, Serbia

<sup>4</sup> Institute for Pathology, Belgrade, Serbia

**Objective:** The aim of the study was to evaluate the choice of optimal therapeutic approach and prognostic factors in children with Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS).

**Patients and Methods:** Between 1997 and 2010, 24 patients with NRSTS, with the median age 15 (range 3 to 18 years) were treated and analyzed for survival. The most common histotypes were synovial sarcoma (29,17%) and malignant peripheral nerve sheath tumour (29,17%). Sixty six percent were presented on the extremities. We diagnosticated 8,3% of patients with metastatic disease, 1 patient with pulmonary metastases and 1 with lymph nodal involvement. Tumour size greater than 5 cm was diagnosticated in 75% of patients. Patients were treated by using of multimodality therapeutic approach including surgery, chemotherapy and radiotherapy. Surgery was the mainstay of the treatments. Radiotherapy was administered to 70,8% and chemotherapy to 91,6% patients (45,8% neoadjuvant chemotherapy).

**Results:** During the median follow up of 60,5 months (6 to 175 months), 5 years overall survival was 71.6% and the disease free survival was 57%. It was possible to perform radical resection after neoadjuvant therapy in 50% of patients with primary unresectable tumours. The prognostic factors such as tumour size  $\geq 5$ cm, invasiveness, positive microscopic margin, high-grade tumors, were not predictive of survival but this must be taken with certain reserves due to small number of patients in our serie.

**Conclusion:** Results indicate that stage, tumour size and radical surgery played the key role in treatment of NRSTS. Prospective randomized trials are needed to quantify the contribution of chemotherapy and to determine the ideal regimen.

<sup>1</sup> Parisini Federica, <sup>1</sup> Benedetti MariaGrazia, <sup>1</sup> Mignani Annarosa, <sup>1</sup>Gaiba Mario, <sup>2</sup>Leardini Alberto, <sup>3</sup>Manfrini Marco.

<sup>1</sup>Physical Medicine and Rehabilitation Unit, <sup>2</sup>Movement Analysis Laboratory, <sup>3</sup>Orthopaedic and Traumatologic Clinic for Musculo-skeletal Tumors, Istituto Ortopedico Rizzoli. Bologna. Italy.

**Objectives stating concisely why the study was conducted:** In the post-surgical period, Partial Weight Bearing (PWB) is early prescribed to patients subjected to Limb Salvage Surgery (LSS) in order to counteract their expected reduction of physical activities. PWB stimulates osteoblasts preventing osteoporosis, a known collateral effect that can possibly occur after chemotherapy, and also preserves biological implants. We have conducted this pilot study in order to verify how much patients comply with verbal instructions given by the physical therapist with regard to walking with PWB using a biofeedback device, and also to check the extent to which these instructions are useful to stimulate the patient to follow the prescribed PWB.

**Materials and Methods:** The device used for the biofeedback is the Pedar Mobile System (Novel<sup>GmbH</sup>, Munich, Germany), which implies the use of flexible and size-adaptable insoles with 99 capacitive sensors. Eleven patients (7 females, 4 males, mean age 26.5) with primitive bone tumors in the lower limbs, who received LSS were recruited. PWB was prescribed to them in various amounts in post-surgery rehabilitation. The load actually applied on the affected limb using the biofeedback device was measured in three conditions within a single experimental session: 1) during a Free Walking phase; 2) during a Conditioning phase in which patients walked with PWB with the audio-feedback device; 3) during Post-conditioning phase without audio-feedback.

**Results:** During the Free Walking phase, 8 patients exceeded on average the prescribed PWB from a minimum of 8,9 N up to a maximum of 144,9 N. Loads from the remaining 3 patients were on average lower than the prescribed ones from a minimum of 28,7 N to a maximum of 83,8 N. All patients, except two, did not exceed on average the prescribed PWB, the measured load being within the two thresholds during the Conditioning phase. During post-conditioning phase, 4 out of the 8 patients who completed this experimental session, did not exceed on average the prescribed PWB, the load remaining below it and within the two thresholds. Four patients still exceeded on average the prescribed PWB, though less than during Free Walking.

**Conclusions:** The audio-feedback device, used to stimulate walking with PWB, allowed more adherence between the load actually applied on the affected limb by the patient and the correspondent prescribed. This adherence is also maintained in the short term even without the audio-feedback. This is of relevance when PWB has a clear clinical significance on bone remodelling or implant fixation.

## TREATMENT OF NON RESECTABLE RARE LOCALIZATIONS OF EWING SARCOMA/PNET IN ADULTS

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Ristic D., Milanovic N., Puric M., Luic N., Sopta J.

**OBJECTIVE:** To examine the efficacy of an intensified induction regimen (vincristine, ifosfamide, doxorubicin, and etoposide [VIDE]) in patients with newly diagnosed Ewing's family of tumors (EFT) localized on head and trunk .

**PATIENTS AND METHODS:** Fourteen patients (ten male and four female patients) entered the study in period between June 2007 and July 2011. Median age was 30 years (18 to 57 years). Two patients had primary tumor localized on head (parietal bone and jaw) , four patients had primary tumor of spine, five patients had pelvis tumor, one patient had tumor of kidney, one had rib cage and one had scapula as primary tumor localization. Three patients had metastatic disease, two with single lung metastases and one with breast metastasis, at the time of diagnosis . All patients were treated with VIDE (vincristine 1.4 mg/m<sup>2</sup> (maximum 2 mg) on day 1, doxorubicin 20 mg/m<sup>2</sup>, ifosfamide 3 g/m<sup>2</sup> plus mesna and etoposide 150 mg/m<sup>2</sup> on days 1 to 3) with growth factor support. Cycles were given every 21 days for up to six cycles. After induction therapy all patients with response were treated with radiotherapy at the tumor bed in CR or at residual tumor in PR.

**RESULTS:** Sixty eight cycles of VIDE were given. Four patients did not completed all six cycles (two because of encephalopathy ,one renal toxicity and one hematological toxicity). Response rate was 78% (95% CI 52.41-92.43) .Five complete remission and 6 partial response were registered according to RECIST criteria . Three patients had progression of disease during therapy with development of metastatic disease. Median follow up was 22 months (range 3-54 months) . Overall survival was 23 months (95% CI ) with six patients still alive.

**CONCLUSION:** Our study suggests that VIDE is an effective induction regimen in treatment of non resectable Ewing Sarcomas of trunk and head. Local control in patients with partial response to induction therapy still remains open question.



## RETROSPECTIVE ASSESSMENT OF THE CHANGE IN INTRA-OSSEOUS INVOLVEMENT IN EWING SARCOMA OF LONG BONES AFTER NEO-ADJUVANT CHEMOTHERAPY; ITS IMPACT ON SURGICAL PLANNING AND LOCAL CONTROL.

Ahmed M. El Ghoneimy\*, Magdy El Sherbiny, Amal Refaat, Iman Zaky, Manal Amin, Hala Taha, Iman Gouda, Mohamed saad.

\*Consultant Orthopedic Oncology, Children Cancer Hospital, Cairo, Egypt.

**Objective:** A retrospective study to compare between the length of intra-osseous extent of Ewing sarcoma of long bones in the initial and the pre-operative MRI, and to correlate between the MRI evaluation and the surgical planning, surgical margins and incidence of local failure.

**Material and methods:** Since the year of 2007 and up to 2010, 38 cases of Ewing sarcoma of long bones were treated by chemotherapy and surgery, in the Children Cancer Hospital in Egypt. Two patients were excluded from the study: one was lost to follow-up and the other had no initial MRI for evaluation, leaving a total number of 36 patients to be evaluated.

The initial (at presentation) and pre-operative MRI studies were reviewed for all cases. The intra-osseous extent was best measured in the T1 sequence with no contrast. The operative notes, surgical margins, and local relapses were reviewed for all cases until the latest follow-up.

**Results:** Twenty-two patients (61.1%) had their MRI measurements (intra-osseous extent) unchanged after neo-adjuvant chemotherapy. In the remaining 14 patients, the difference between the initial and pre-operative MRI was restricted to 1 to 1.5 cm less tumor involvement as seen in the pre-operative MRI.

The initial MRI was used for pre-operative planning in 8 cases and the post-chemotherapy MRI in 28 cases. The surgical margins were negative in all cases except one case in which the marrow margin was positive and the patient received post-operative radiotherapy. Until the latest follow-up (median follow-up period 19 months) only one patient had a local recurrence. The initial surgical margins of this case were negative.

**Conclusion:** Following chemotherapy for Ewing sarcoma of long bones, MRI measurements of bone extent do not change much when comparing the initial to the pre-operative MRI.

The use of the pre-operative MRI in the surgical planning, did not lead to a higher incidence of positive margins and local failure.

Although, this study has the limitation of a short follow-up period (median of 19 months), the incidence of local failure is highest in the first two years following surgery as reported in the literature.



Graci C, Perisano C, Spinelli MS, Valenzi E, Di Giacomo G, Fabbriciani C, Maccauro G

Department of Orthopaedics and Traumatology, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

**Objective:** In lung cancer patients, metastases to soft tissues (STs), including the skeletal muscle, subcutaneous tissue and skin, are rarely reported. Besides, lung cancer, primary carcinomas of the kidney and colon are the most commonly associated with ST metastases. The aim of the study is to determine the prevalence, clinical-pathological features and treatment options of ST metastases originating from lung carcinoma.

**Materials and Methods:** A literature search was performed using the following terms: lung cancer, ST metastasis, skeletal muscle metastasis, cutaneous metastasis, subcutaneous metastasis.

**Results:** Autopsy series have detected soft tissues metastases in 0.75-9% of patients who died from metastatic lung carcinoma. Pain and the presence of a palpable mass are the most frequent clinical features. The biopsy is recommended after MRI for diagnosis. Due to the infrequency of ST metastases, the differential diagnosis must be done especially with ST primary sarcomas. The type of treatment depends on the clinical picture and prognosis and includes observation, radiotherapy, chemotherapy and surgery.

**Conclusions:** In lung cancer patients, ST metastases are rare, but not exceptional. Their presence should be suspected in the presence of a palpable mass either painful or asymptomatic. Radiological and histological examinations are required for the definite diagnosis. The choice of treatment should be based on considerations related to the stage of the primary tumor and the patient's global health status.

Cosker T, Ohringer G, Porter C, Whitwell D, Sharpley F, Gibbons M

Of the Nuffield Orthopaedic Centre, Oxford, UK

**INTRODUCTION:** Estimates from the National Cancer Network suggest that approximately 3,000 patients are diagnosed with sarcoma annually in the UK. Soft tissue sarcoma occurs at any age and are common in those of working age. The financial impact for patients with a diagnosis of sarcoma is significant. Treatment is undertaken in specialist regional centres and patients may have to travel significant distances for ongoing treatment. The disease process and time away from work for appointments may have an adverse effect on employment.

**METHODS:** Patients attending the Oxford Sarcoma Service between June 2010 and June 2011 were questioned about the distance they had had to travel to the clinic, the mode of transport they used to get there, the associated costs incurred whilst visiting the hospital (such as car parking), and any other relevant costs associated with treatment. They were also questioned with regard their occupation and the amount of time they had had to take away from work as a result of their diagnosis as well as whether they felt that their chances of promotion or career progression had been adversely affected.

**RESULTS:** There were 93 patients, of which 45 (48%) had benign disease and 48 (52%) had malignant disease. 54 (58%) were employed, 33 (36%) were unemployed. On average, patients had to make a return journey 62 miles for every visit to the hospital (max 188 miles). Patient's employment was more likely to be affected and their partners more likely to take time off work if they lived further away from the hospital ( $p=0.021$  and  $p=0.028$  respectively). For the 75 patients who came to hospital by car, the mean total cost of travel was £414. This includes an average cost of £29.60 associated with every outpatient appointment. Patients with malignant disease experienced significantly higher total costs £608 vs. £205 ( $p<0.001$ ) when compared with those with a benign diagnosis. The highest cost incurred by a single patient was £4364.

**DISCUSSION:** Whilst the treatment of bone and soft tissue sarcoma is increasingly well understood, little has been written on the financial impact for patients undergoing treatment. This study shows that for patients of working age treatment at a specialist centre has a significant financial impact. In addition there is a significant effect on employment and career progression.

## FUNCTIONAL OUTCOME FOLLOWING EXCISION OF LARGE VOLUME SOFT TISSUE SARCOMA INVOLVING THE SCIATIC NERVE : 13 YEAR RESULTS

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Tom Cosker\*;Stephen Gwilym;Stephen McDonnell;Nic Athanisou;Takeshi Kashima;Bass Hassan;Duncan Whitwell;Max Gibbons

Tumour Oncology, Nuffield Department of Orthopaedic Surgery, Oxford, UK

**Introduction:** Our Unit has been treating large volume soft tissue sarcomas involving the sciatic nerve with epineurectomy for over a decade. The aim of this study was to quantify the functional outcome of patients who were known to have sciatic nerve involvement pre-operatively and went on to have nerve preserving surgery utilising a planned marginal excision with epineurectomy.

**Methods:** 36 patients with soft tissue sarcomas involving the sciatic nerve were studied treated between 1997 and 2010. Nineteen underwent surgery with extended epineurectomy of the sciatic nerve and planned marginal excision. All patients underwent staging and follow up at our Sarcoma Clinic with functional assessment and TESS evaluation.

**Results:** There were twenty six low / intermedite and ten high grade posterior thigh tumours . Two were recurrent and eighteen were primary. There were thirteen men and twenty three women with a mean age of 74 years. Thirty five patients underwent planned marginal excision. There was soft tissue reconstruction in three cases using fascial adductor or gracilis graft for sciatic nerve cover and one with superficial femoral nerve and vein resection requiring ipsilateral saphenous reconstruction. The remainder underwent direct primary reconstruction. Eighteen patients underwent post operative radiotherapy. There was no local recurrence of disease. There was one patient with post radiation wound necrosis that resolved. Four patients have died of unrelated causes.

**Discussion:** Planned marginal excision (PME) of low grade large volume posterior thigh sarcomas with extensive sciatic nerve involvement can be successfully treated with preservation of the sciatic nerve without significant morbidity and excellent resultant limb function. Even with PME of high grade disease with adjuvant radiotherapy, there was no local recurrence. Whilst the procedure is technically demanding, providing strict surgical technique is employed, damage to the sciatic nerve is rare and leaves patients with an unimpaired future lifestyle.

Martynkov DV, Kharatishvili TK, Bohyan BJ, Burov DA, Aliev MD

FGBU N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences

Moscow, Russian Federation

**Objective:** To analyse prognostic factors associated with local recurrence of soft-tissue sarcomas

**Materials and methods:** 228 patients with recurrent soft tissue sarcomas were treated in RCRC RAMS in 2000-2010 years. There were 112 (49,1%) male and 116 (50,9%) female, with a age of  $42,9 \pm 15,3$  years (range 16-77). Tumor size was: <5 cm – 39,5%; 5-10cm – 32%; >10 cm – 28,4%. Histological types were: malignant fibrous histiocytoma – 27,2%, liposarcoma – 19,8%, synovial sarcoma – 18,5%, malignant peripheral nerve sheath tumors – 19,8% , leiomyosarcoma – 7,7% and others. G3 – 69,1% of cases, G2 – 27,2% and G1 – 3,7%. Time to local recurrence: <6 months – 39,5% of patients, 6-12 months – 24,7%, 12-24 months – 18,5% and >24 months – 17,3%. Also we analysed surgical margin (intralesional, marginal, wide, radical), location in the anatomic compartments. The prognostic influence of clinicopathological characteristics on disease-specific survival were examined by univariate and multivariate analyses.

**Results:** The mean follow-up was 41,7 ranged from 2,1 to 161,2 months. The overall 5-year survival was 69%. Tumor size, tumor grade and short time to local recurrence (<6 months) are independent factors for disease-specific survival ( $p < 0.05$ ) in univariate and multivariate analyses.

**Conclusion:** Patients with large high-grade rapidly growing tumors require a more active approach to treatment, with the inclusion of systemic chemotherapy. We continue the clinical development of staging system for patients with isolated local recurrence for the formation of subgroups of patients with different survival rates and rational treatment based on their prognosis.

# INFLUENCE OF UNUSUAL METASTATIC COURSES IN SOFT TISSUE SARRCOMAS ON THE TYPE AND EXTENT OF SURGERY

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Matějovský, Z.<sup>1</sup>, Lesenský J.<sup>1</sup>, Kofránek I.<sup>1</sup>, Krystlík Z.<sup>1</sup>, Matějovská J.<sup>2</sup>, Frajer L.<sup>2</sup> Povýšil C.<sup>3</sup>

<sup>1st</sup> Medical School, Charles University, Teaching Hospital Bulovka, Prague, Czech Republic –Orthopedic Clinic<sup>1</sup>, Clinic for plastic surgery<sup>2</sup>, Institute for pathologic anatomy<sup>3</sup>.

**Materials and methods:** We retrospectively evaluated over 300 patients with malignant soft tissue sarcomas considering the patterns of local and regional disease relapses together with the resection margins and adjuvant treatment. LG liposarcomas were excluded.

**Results:** We had two groups with over 100 patients with synovial sarcomas and malignant fibrous histiocytomas (MFH). Other larger groups with over 20 patients were diagnosed as neurogenic tumors and leiomyosarcomas.

In synovial sarcoma located as deep tumors mainly in the foot we observed bone skip lesions. Such bone lesions usually progressed systematically. Superficial synovial sarcomas relapsed usually as skip lesions into subcutaneous tissue. Such affections if further excised usually did not progress systemically. In deep MFH skip lesions in adjacent compartments were connected with bad prognosis for systemic spread and survival. On the contrary superficial MFH recurred repeatedly as skip lesion into the subcutaneous tissue without systemic spread. This occurred first if the tumor skipped into deep tissue. Deep dedifferentiated HG liposarcomas were connected with skip lesions in adjacent compartments while leiomyosarcomas were connected with lymphatic and distal metastases, even into bones or distant soft tissues. Interesting were 3 cases of clear cell sarcomas which all relapsed through LN further systematically.

**Conclusion:** MFH and synovial sarcomas in superficial locations usually spread with skip lesions into adjacent subcutaneous tissue which do not further progress systematically and therefore thorough controls and early wide excisions of such lesions are a good treatment option. Once they progress into deep tissue ablative surgery should be considered. For such primary superficial lesions we recommend wider margins of at least 3 to 5 cm with secondary closure with skin grafts or flaps. If presented in deep location biopsy with preoperative treatment of either chemotherapy or radiation of the whole compartment should be considered to prevent relapse into the same or adjacent compartments. Even wide excisions of the whole muscle do not warranty local control as skip lesions into the adjacent muscles are to be expected and ablative surgery should be considered in such cases if no systemic spread is presented. In bony involvement of synovial sarcoma ablative surgery should be strongly recommended.

Metastases of leiomyosarcomas can be controlled with combined wide excision and systemic treatment and/or radiation on lymph nodes. Nevertheless skip lesions within 5 cm around the scars were repeatedly observed in subcutaneous tissue and therefore resection of the whole skin and subcutaneous tissue covering the tumor with reconstruction of the skin defect should be preferred.

Clear cell sarcoma in our experience always showed a systemic relapse first through lymph nodes. Primary lymphadenectomy with radiation should be therefore considered. Nevertheless histological differential diagnosis of such tumors is very difficult.

Burov DA, Bohyan BJ, Martynkov DV, Aliev MD

FGBU N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences

Moscow, Russian Federation

**Objective:** To identify the most significant prognostic factors in the prehospital phase for further local recurrence of soft tissue sarcomas of the locomotor apparatus.

**Materials and methods:** We analysed 168 patients with extremity soft tissue sarcomas treated in the Cancer Research Center in 2000-2010 years. Gender distribution was as follows: 87 were male (51.2%), 83 were female (48.8%). Mean age  $52,16 \pm 18,36$  years, range 22-85 years. All patients were initially examined not in the sarcoma centers. The primary diagnosis at any medical facility was soft tissue sarcoma (group A, 73 cases, 43.4%) or others (group B, 95 cases, 56.5%): inflammation - 26 (15.5%), benign tumors - 20 (11.9%), hematoma - 13 (7.7%), venous thrombosis - 13 (7.7%), hernia - 3 (1.8%), etc. Patients before entering the RCRC received in the group A specific treatment in 71 cases (42%). In the group B patients received symptomatic treatment in 64 cases (38.1%). After reviewing all cases in the Cancer Research Center, sarcoma was founded in 100% of patients. Distribution of patients according to tumor size and depth were: T1a - 7 patients (4.1%), T1b - 2 (1.1%), T2a - 5 (2.9%), T2b - 154 (91%). The most frequent tumors were G3 - 82% of cases. The distribution by histological type of tumor: malignant fibrous histiocytoma - 18.4%, liposarcoma - 17.2%, synovial sarcoma - 16.7%, rhabdomyosarcoma - 10.2% and others. Time from diagnosis to the treatment facility before entering the RCRC is in the range from 1 to 7 months.

**Results:** Median follow-up of patients - 65 months. In the group B mean time to correct diagnosis was 5,5 months. In the group A a local recurrence rate was 16%. In the group B (with the initial incorrect diagnosis) the level of local recurrence - 37%, and resection R1 was dominated during operations. The 5-year overall survival was 75% and 62% in group A and group B respectively.

**Conclusions:** It was noted a significant increase in local recurrence in group B. In most of these cases have been difficulties with the treatment. An analysis of errors and complications in the diagnosis and initial treatment of soft tissue sarcomas can improve the quality of the procedures to determine the most important aspects influencing the subsequent recurrence.

# INTRABDOMINAL METASTASIS IN OSTEOSARCOMA: EXPERIENCE OF A SINGLE CENTER

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1 Kebudi Rejin, 2 Özgüven A. Aykan, 1 Görgün Ömer, 3 Yekeler Ensar, 4 Bilgiç Bilge, 1 Ayan İnci, 5 Özger Harzem,

Istanbul University, 1Cerrahpaşa Medical Faculty & Oncology Institute, Department of Pediatric Hematology and Oncology; 2 Istanbul Faculty of Medicine, Department of Pediatric Hematology and Oncology, 3 Department of Radiology, 4Department of Pathology, 5Department of Orthopaedics

**Objectives:** Extra-pulmonary metastasis, particularly abdominal metastasis from osteogenic sarcoma are rare and generally appear as a solid mass of calcification as the primary tumor. The aim of this study is to document the incidence, characteristics, treatment, prognosis of abdominal metastasis in osteosarcomas in a single institution and to review the literature.

**Methods:** From September 1989 to December 2002, 94 children < 16 years of age with osteosarcomas were diagnosed and treated in the Division of Pediatric Oncology, Oncology Institute, Istanbul University. Patients with abdominal metastases were assessed.

**Results:** Two girls of 94 patients (2.1 %) with osteosarcoma developed abdominal metastases. One had pulmonary metastasis at diagnosis and the other had developed lung metastasis 15 months after diagnosis. They developed abdominal metastasis 4 and 3 years after diagnosis during therapy or relapse at a median duration of 16 (1-70) months from initial diagnosis. All patients had metastases to various sites, mostly lung, at the time the abdominal metastases were detected. Treatment included surgery, and chemotherapy (CT) in 1, S in 1. Both patients died at a median time of 2 months (2 days- 6 months) from the time of abdominal metastasis with progressive disease. Brain metastasis have also been reported especially in patients who had lung metastasis at diagnosis and in our series the incidence was 1.45 % (Kebudi R et al, Neurooncology 2005).

**Conclusions.** Abdominal metastasis in osteosarcoma is a rare event, but the abdomen should be investigated in case of recurrence from osteosarcoma. The outcome for these patients is dismal in this series and in the literature. Children with metastatic osteosarcoma who develop abdominal pain or any other gastrointestinal symptom should be investigated for possible abdominal metastasis.

**Key words:** Osteosarcoma, abdominal metastasis



T. Nakamura, C. Gaston, A. Abudu, L. Jeys, R. Tillman, S. Carter, R. Grimer

*Institution; Oncology Unit, The Royal Orthopaedic Hospital, Birmingham city, United Kingdom*

**Introduction:** Anaemia is a common finding in cancer patients. Anaemia is associated with shorter survival times for many cancers. Recently, several studies demonstrated that interleukin-6 could be a mediator of cancer-related anaemia, which induces the production of C-reactive protein (CRP). The aims of this study were to investigate the relationship between anaemia and CRP and to determine whether anaemia before treatment predicts the overall survival and disease-free survival in patients with newly diagnosed non metastatic soft tissue sarcoma (STS).

**Methods:** A total of 376 primary STS patients treated between 2003 and 2010 were retrospectively reviewed. All patients were treated with surgery and adjuvant radiation therapy when indicated. The Haemoglobin (Hb) levels were obtained before treatment for all patients. According to World Health Organization (WHO), we defined anaemia when Hb levels were less than 13g/dl for male and 12g/dl for female, respectively. The mean age at diagnosis was 59 years. There were 221 male and 155 female patients. The mean follow-up period was 32 months.

**Results:** Anaemia was seen in 117 patients (31%). The histological grade, age, tumour size, depth and pre-treatment CRP levels were related to anaemia. Hb levels were strongly correlated with CRP levels (spearman's  $r = -0.54$ ,  $p < 0.0001$ ). Patients with anaemia had a poorer overall survival than patients without anaemia ( $p < 0.0001$ ). The overall survival estimates at 5 years were 53.4% versus 79.6%, respectively. Patients with anaemia had also poorer disease-free survival than patients with normal CRP levels ( $p < 0.0001$ ). The disease-free survival estimates at 5 years were 45.0% versus 66.0%, respectively. Multivariate analysis showed that pre-treatment anaemia was an independent predictor of disease-free survival ( $P = 0.04$ ).

**Conclusions:** Pre-treatment anaemia was related to CRP levels. Anaemia was found to be a poor prognostic factor for overall survival in a univariate analysis and for disease-free survival in a multivariate analysis for STS patients.

## EXTENDED EXPERIENCE WITH AN ADJUVANT SANDWICH CHEMO-RADIO-CHEMO-THERAPY CONCEPT FOR HIGH-RISK ADULT SOFT TISSUE SARCOMAS

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Kerkhoff, S. Bröckling, R. Liersch, J. Hards, G. Gosheger, H.-T. Eich, P. Tschanter, U. Krug, M. Pohlen, A. Hilbig, C. Pohlkamp, C. Schulz, R. M. Mesters, C. Müller-Tidow, T. Kessler and W. E. Berdel

Department of Medicine, Hematology and Oncology, Department of Orthopedic Surgery and Department of Radiation Oncology, Albert-Schweitzer-Campus 1, 48149 Muenster, Germany

**Purpose:** Surgery and radiation therapy represent the standard treatment of localized high-risk soft tissue sarcomas (STS), while the significance of adjuvant chemotherapy is discussed controversially. Our single center phase II trial had shown a favourable long-term survival with low distant recurrence and acceptable toxicity for patients treated with a sandwich chemo-radio-chemotherapy concept. We present our extended experience and analysed further patients treated subsequently to the study with an identical protocol.

**Patients and Methods:** From 1997 to 2012 forty-three patients with localized, completely resected ( $R_0$ ) high risk STS were accrued to this analysis. Twenty-seven patients were analysed in our prospective study, while sixteen patients were analysed subsequently. All patients were treated with a sequence of surgery, adjuvant chemotherapy and interposed radiotherapy. Within a median time of 33.9 days after surgery they received a chemotherapy consisting of doxorubicin ( $75 \text{ mg/m}^2 \text{ d1q 3w}$ ) and ifosfamide ( $5\text{g/m}^2\text{d1q3w}$ ) in 4 cycles. Between cycle 2 and 3 radiotherapy (total dose of 50.4 Gy fractionated plus boost of 10 Gy) was administered.

The patients were followed up with regard to remission status and long-term toxicity.

**Results:** Data of all patients with a minimum follow-up of 5 months from diagnosis showed an EFS of 70.7 % and an OS rate of 80.5 %. Of the 27 patients treated in our phase II study, 81.4 % are still alive and in complete remission at a median follow-up of 107.8 months (22-164 months). There was no long term toxicity. The 16 patients subsequently treated and analysed had a median follow up of 32 months (range 5-80 months) with an OS of 87.5%. Therapy-related toxicity was mild.

**Conclusion:** Sandwich chemo-radio-chemotherapy after  $R_0$  resection offers a promising rate of long-term remission by a short term combined treatment with a low toxicity profile. Future multicenter studies are warranted.

A. George; R. Grimer

Royal Orthopaedic Hospital, Birmingham, UK

**Introduction:** Delays in diagnosis are common for patients with bone and soft tissue sarcoma (STS). This is despite referral guidelines produced by the Department of Health and NICE more than a decade ago.

**Objectives:** This study set out to identify the early symptoms experienced by patients with sarcomas and reasons for delays in making a definitive diagnosis. We proposed to evaluate symptoms experienced against current guidelines for referral to determine whether amendment might improve direct referral rates for patients.

**Methods:** Retrospective interviews were carried out with 107 patients with bone sarcoma (41 patients) and STS (66 patients) presenting to a specialist centre. We determined initial symptoms experienced prior to definitive diagnosis and occurrence of patient and doctor delays in reaching specialist care.

**Results:** Median patient delay was 1 month whilst doctor delay was 3.2 months from first symptoms to diagnosis for all sarcomas. Forty-nine patients (74%) with STS initially presented to their GP with at least one guideline feature to prompt urgent referral. Only 2 patients (4%), however, were referred directly to a sarcoma unit with 21 (43%) referred to secondary care for investigation. Patients with a lump increasing in size exhibited longer patient delays whilst doctor delay was shorter for deep lumps. Thirty-six patients (88%) with a bone sarcoma initially presented with symptoms to prompt further investigation. However, significant delays (3.9 months) were seen in reaching specialist care. Only 4 patients (10%) were referred directly to a sarcoma unit at first presentation with 21 patients (54%) referred for further investigation elsewhere.

**Conclusions:** It is evident that awareness and referral of sarcomas remains poor. We suggest specific amendment to current guidelines and clearer referral pathways for patients. Furthermore, the need for robust education strategies, predominantly amongst healthcare professionals is indicated in order to promote greater awareness to potentially malignant lesions.

## USEFULNESS OF $^{18}\text{F}$ -FDG-PET/CT IN DIFFERENTIATING BETWEEN BENIGN AND MALIGNANT SOFT TISSUE TUMORS

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Manabu Hoshi, Jun Takada, Naoto Oebisu, Masanari Aono, Makoto Ieguchi, Hiroaki Nakamura

Department of Orthopedic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-Machi, Abeno-Ku, Osaka 545-8585, Japan

**Objective:** Integrated 2-deoxy-2- $^{18}\text{F}$ -fluoro-D-glucose positron emission tomography combined with computed tomography ( $^{18}\text{F}$ -FDG-PET/CT) evaluates both tumor function through glucose metabolism, and morphological features through CT imaging. The aim of the current study was to evaluate the usefulness of  $^{18}\text{F}$ -FDG-PET/CT for preoperative differential diagnosis between benign and malignant soft tissue tumors.

**Materials and Methods:** The criteria for diagnosis of malignancy on  $^{18}\text{F}$ -FDG-PET/CT, was defined as the soft tissue tumor having a maximum standardized uptake value (SUV max) over 2.0 on PET, and the greatest diameter being more than 5cm measured on CT. A total of 122 patients with soft tissue tumors were examined by  $^{18}\text{F}$ -FDG-PET/CT, prior to histopathological diagnosis.  $^{18}\text{F}$ -FDG-PET/CT,  $^{18}\text{F}$ -FDG-PET, and CT were separately evaluated, to determine the usefulness of each imaging modality.

**Results:** The patients consisted of 64 males and 58 females, ranging in age from 17 to 91 years ( $57.9 \pm 16.1$  years). Pathological diagnosis revealed 101 malignant and 21 benign lesions. The sensitivity, specificity, and accuracy for the cut off value of SUV max over 2.0 on PET, were calculated to be 85.9%, 29.0%, and 68.3%. Those for tumor size being over 5cm on CT, were 82.3%, 30.0%, and 69.7%. Those of integrated  $^{18}\text{F}$ -FDG-PET/CT were 82.2%, 33.3 %, 79.8%, respectively.

**Conclusions:** Integrated  $^{18}\text{F}$ -FDG-PET/CT was more accurate for the differential diagnosis between benign and malignant soft tissue tumors, compared with  $^{18}\text{F}$ -FDG-PET and CT alone.

# THE CLINICAL VALUE OF C-REACTIVE PROTEIN AND COMORBIDITY IN PREDICTING SURVIVAL OF PATIENTS WITH HIGH GRADE SOFT TISSUE SARCOMA

018

Tomoki Nakamura<sup>a</sup>, Matthew Francis<sup>b</sup>, Jackie Charman<sup>b</sup>, Louie Gaston<sup>a</sup>, Lee Jeys<sup>a</sup>, Robert Grimer<sup>a</sup>

<sup>a</sup>The Royal Orthopaedic Hospital, Birmingham, United Kingdom

<sup>b</sup>West Midlands Cancer Intelligence Unit, Birmingham, United Kingdom

**Aims:** The aim of this study was to determine whether C-reactive protein (CRP) levels and co-morbidity before treatment predict the overall survival and local tumour control in patients with high grade non-metastatic soft tissue sarcoma (STS).

**Methods:** A total of 332 adult patients were retrospectively reviewed. The CRP levels were obtained before treatment for all patients. Co-morbidity was evaluated by using the Charlson co-morbidity Index (CCI). The patients who were referred for additional resection were excluded from this study.

**Results:** Elevated CRP levels were seen in 152 patients (range; 11-342mg/L, average; 75mg/L). The histological grade, age, tumour size and AJCC stage were significantly higher than those in patients with normal CRP levels. CCI score varied from 0 to 4. 265 patients had a score of 0 (no identified co-morbidity), and 67 patients had a score of 1 or more. Age in patients with identified co-morbidity was significantly higher than those in patients with no-identified co-morbidity. Patients with elevated CRP levels (>10mg/L) had a poorer overall survival than patients with normal CRP levels ( $p<0.0001$ ). The overall survival estimates at 5 years were 42.2% versus 81.8%, respectively. Patients with elevated CRP levels had also poorer local tumour control rate than patients with normal CRP levels ( $p=0.0004$ ). The local tumour control rate estimates at 5 years were 74.5% versus 89.0%, respectively. Multivariate analysis showed that pre-treatment CRP levels were a strong independent predictor of survival ( $p<0.0001$ ) and local tumour control ( $p=0.04$ ).

**Conclusions:** Pre-treatment CRP level could be a marker of tumour aggressiveness and is a strong predictor of survival for STS.

# USEFULNESS OF CONTRAST COLOR DOPPLER ULTRASONOGRAPHY IN PREOPERATIVE DIFFERENTIAL DIAGNOSIS BETWEEN MALIGNANT AND BENIGN SOFT TISSUE TUMORS

019

Naoto Oebisu, Manabu Hoshi, Jun Takada, Hiroaki Nakamura,

Dept. of Orthopaedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan

**Purpose:** The aim of the present study was to elucidate the usefulness of contrast enhanced color doppler (CD) ultrasonography for preoperative differential diagnosis between benign and malignant soft tissue tumors.

**Material and Methods:** The CD ultrasonography was applied to 76 patients with soft tissue masses for preoperative diagnosis prior to histopathological diagnosis. Blood-flow in the masses were evaluated and compared between benign and malignant lesions. Conventional criterion, according to classical Giovanglion classification was used for evaluation, with or without contrast medium, Sonazoid. The elasticity of the tumor was also measured, and compared with normal fat tissue, using elastography. Student's t-test was used to compare differences between benign and malignant soft tissue tumors.

**Result:** A total of 44 benign and 32 malignant soft tissue tumors were included in the present study. Contrast medium was used to evaluate blood-flow in 27 masses (14 benign and 13 malignant). Elastography was performed in 37 masses (24 benign and 13 malignant). In differentiating malignant tumors from benign, the sensitivity, specificity and accuracy of CD with Sonazoid were respectively 92.3%, 69.2% and 68.0%; while those without Sonazoid were respectively 53.1%, 78.6% and 81.5%. Elastic ratio average was 0.56 in benign and 0.21 in malignant tumors ( $P=0.004$ ).

**Conclusion:** High accuracy of contrast enhanced CD, in distinguishing malignant from benign soft tumors, was confirmed. The result of this analysis indicates the usefulness of contrast enhanced CD for preoperative diagnosis in soft tissue tumors.

G. Ulrich Exner and Charles E. Dumont  
orthopaedie zentrum zuerich, Zurich, Switzerland

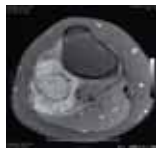
**Introduction:** For most musculo-skeletal sarcomas complete resection with uncontaminated margins R0 resection) is still the most important part of treatment. For preservation of limbs and especially joints the margins may be critically small. The precision of osteotomies controlled under standard X-ray or image intensifier control is influenced by parallax and the limitation in 3-dimensional analysis of oblique planes.

**Objectives:** Mobile CT scanners to provide real time 3D images during surgery are produced (e.g. the Oarm Medtronic) but because of the high cost not yet readily available. We have therefore used to place marks (K-wires or ancre) in Standard CT-scanners immediately ort he day before surgery.

**Method - Case example:** 17 year old girl, osteosarcoma of the proximal fibula involving the tibio-fibular joint and large contact with the tibia. Following the neoadjuvant chemotherapy the day before the definitive tumor resection 3 K-wires were placed under CT-control to guide the osteotomies of the tibia (1st above the tibio-fibular joint, 2nd oblique proximally, 3rd oblique distally into the tibia). The resection then was performed letting the K-wires guide the saw blade avert from the tumor. The tibial plateau was supported by an allograft. Because of the resection of the involved fibular nerve tendon transpositions were performed simultaneously. Examination of the tumor revealed uncontaminated margins and the patient presently one year after surgery is diseasefree.



preoperative MRI



postop. X-Ray



1st prox. transverse



2nd prox. oblique



3rd dist. oblique CT marking

**Results:** Using different CT-assisted modes in performing tumor resection (placing markers in the CT as guides for resection or using CT navigation) allows to perform resections with a precision in the range of mm.

**Conclusion:** In situation where intraoperative determination of planes, axes or points maybe difficult and real time CT is not available setting of pre-operative marks under CT-control maybe useful.



## THE ROLE OF SOMATOSTATIN RECEPTOR SCINTIGRAPHY (SRS) ON THE DIAGNOSIS OF DESMOID TUMORS

030

Joerg Friesenbichler<sup>1</sup>, Reingard Aigner<sup>2</sup>, Patrick Sadoghi<sup>1</sup>, Bernadette Liegl-Atzwanger<sup>3</sup>, Werner Maurer-Ertl<sup>1</sup>, Christian Weger<sup>1</sup>, U. Pirker-Frühau<sup>1</sup>, Andreas Leithner<sup>1</sup>.

<sup>1</sup>Department of Orthopaedic Surgery, Medical University of Graz, Austria.

<sup>2</sup>Division of Nuclear Medicine Radiology, Department of Radiology, Medical University of Graz, Austria.

<sup>3</sup>Institute of Pathology, Medical University of Graz, Austria.

**Background:** Magnetic Resonance Imaging is considered as imaging modality of choice in diagnosis of desmoid tumors, though even this technique can lack to distinguish aggressive fibromatosis from other benign or malignant soft tissue tumors.

The aim of this study was to investigate if desmoid tumors would show an adequate tracer uptake in somatostatin receptor scintigraphy and moreover to correlate these results with immunohistochemical staining.

**Patients and Methods:** Thirteen patients with desmoid tumors were examined with somatostatin receptor scintigraphy. Additionally, seven of these patients have been tested for the immunohistochemical expression of somatostatin receptor subtype 2A. The results of somatostatin receptor scintigraphy and the results of immunohistochemical staining (somatostatin receptor subtype 2A) were evaluated and correlated.

**Results:** Somatostatin receptor scintigraphy revealed that eight of 13 affected patients (62%) showed an enhanced tracer uptake. On the other hand, the correlation between the results of somatostatin receptor scintigraphy and immunohistochemical investigations was poor (two out of seven cases)

**Conclusion:** The current study demonstrated that desmoid tumors frequently express somatostatin receptor subtype 2, while immunohistochemical investigations did not correlate with these findings. This may likely be due to lack of standardization of this technique and also due to heterogeneous receptor distribution within the tumors.

# INSULIN-LIKE GROWTH FACTORS (IGF) AND IGF BINDING PROTEINS IN BLOOD SERUM OF BONE TUMOR PATIENTS: INTERRELATION AND POSSIBLE CLINICAL IMPLICATIONS.

N.E.Kushlinskiy, I.V.Babkina, E.S.Gershtein, E.A.Solovykh, I.V.Bulytcheva, Yu.N.Solovyev

Russian N.N.Blokhin Cancer Research Center RAMS, Moscow

**Objectives:** Insulin-like growth factors (IGFs) are multifunctional peptides that regulate cell proliferation, differentiation, and apoptosis, and they are important in both normal and tumor growth. IGF-1 and IGF-2 were isolated from human osteosarcoma and Ewing's sarcoma cells.

**Study Aims:** The goal of our study was to compare serum levels of IGF-1, IGF-2, IGFBP-1 and IGFBP-3 in patients with various bone tumors and healthy donors in order to evaluate possible clinical implication of these factors.

**Methods:** IGF-1, IGF-2, IGFBP-1 and IGFBP-3 concentrations were measured in blood sera of 112 untreated bone tumor patients (malignant - 74 (osteosarcoma - 25, chondrosarcoma - 21, Ewing tumor - 18, malignant fibrous histiocytoma - 5, chordoma - 5), borderline (giant-cell tumor) - 14, benign bone neoplasms - 24) 15–69 years of age, median - 27,5 and from 47 practically healthy subjects 14–63, median - 35 years old by standard direct sandwich ELISA assays (DSL, USA).

**Results:** IGF-1 and IGF-2 levels in healthy patients' sera were statistically significantly lower than in patients with malignant and borderline bone tumors ( $p < 0.05$ ). IGFBP-1 and IGFBP-3 levels in patients with various types of affected bones were higher than in practically healthy subjects. No significant differences in IGFBP-1 concentrations were revealed between various groups of bone tumor patients. The highest IGFBP-3 levels were found in patients with benign bone neoplasms. In practically healthy subjects no significant correlations were revealed between serum levels of the parameters studied. In patients with benign bone neoplasms only positive correlation between serum IGF-2 and IGFBP-3 ( $r = 0,58$ ) was found, and patients with borderline giant-cell tumor were characterized by positive correlation between both IGF-2/IGFBP-3 ( $r = 0,69$ ), and IGF-1/IGFBP-3 ( $r = 0,81$ ) serum levels. Meanwhile, in malignant bone tumors group positive correlation was found between IGF-1/IGF-2 ( $r = 0,51$ ), IGF-1/IGFBP-3 ( $r = 0,58$ ), IGF-2/IGFBP-3 ( $r = 0,63$ ) serum concentrations, and these associations were mostly pronounced in osteosarcoma patients. No significant associations of IGFs/IGFBPs levels with the type of affected bone or tumor histologic type was found. Low serum IGF-2 ( $< 620$  ng/ml) and IGFBP-3 ( $< 3,5$  mcg/ml) were associated with shorter disease-free interval (DFI) in osteosarcoma patients: median DFI in this group comprised 7.25 months, while in patients with higher IGF-2 and IGFBP-3 levels it comprised 15.5 months.

**Conclusions:** Disbalances in IGFs regulatory system in patients with malignant bone tumors as compared to those with borderline and benign bone tumors and practically healthy subjects, and possible prognostic role of serum IGF-2 and IGFBP-3 levels in osteosarcoma patients were demonstrated.

# PROGNOSTIC SIGNIFICANCE OF PRE-TREATMENT C-REACTIVE PROTEIN IN PATIENTS WITH HIGH-GRADE SOFT TISSUE SARCOMAS

063

Monika Jagodic. Institute of oncology, Ljubljana, Slovenia.

**Objectives:** Elevated levels of CRP have been recognized as a prognostic factor in various human malignant tumors. To date there are only few previous reports about the prognostic significance of CRP in patients with sarcomas. So, the primary aim of this study was to assess the prognostic value of pre-treatment CRP in a group of patients with high-grade soft tissue sarcomas.

**Material and methods:** A total of 68 adult patients (35 females, 33 males, with an average age of 56 years) with high-grade soft tissue sarcomas (stage II in 43% of patients, stage III in 57% of patients) were retrospectively analysed. Patients with evidence of distant metastases at the time of primary treatment, smokers and patients with concomitant infection, inflammatory disease or cardio-vascular disease were excluded from this study. 48 (71%) patients had tumors in the extremities, 20 (29%) patients had tumor location in the trunk. Surgical treatment was performed on all 68 patients. 59% of all patients also received radiotherapy. Chemotherapy was given to 12% of patients. After completion of primary treatment, the patients were regularly monitored (median follow-up 43 months, range 4-89 months). Patients' blood to measure the level of serum CRP was obtained before start of treatment as part of a pretreatment clinical routine. A serum CRP level of  $\leq 5$  mg/dl was regarded normal corresponding to our clinical routine practice. Pre-treatment CRP was correlated with pathological and clinical prognostic factors, disease-free survival (DFS) and overall survival (OS) in an uni-variate and multi-variate statistical model.

**Results:** Mean pre-treatment serum CRP was 10.38mg/dl (range 0-75 mg/dl, median 3mg/dl). 25 (37%) patients had CRP levels above the defined cut-off of 5 mg/dl. CRP was significantly associated with histologic grade, tumor stage, recurrent disease and death of underlying malignant disease, but not with patients' age, sex, tumor location, tumor depth or histological type. In univariate Cox analysis of DFS, CRP ( $>5$  mg/dl vs.  $\leq 5$  mg/dl), histological grade (3 vs. 2), tumor depth (deep vs. superficial), tumor stage (III vs. II), age of patients ( $\geq 60$  years vs.  $<60$  years) and adequate surgical margins (non-adequate vs. adequate) were statistically significant prognostic factors. The three-year DFS was only 23% in patients with CRP values  $>5$  mg/dl and 69% in the group of patients with CRP values  $\leq 5$  mg/dl. In multivariate analysis (Cox model) of DFS, CRP ( $p=0.017$ , relative risk (RR) 2.6) and age of patients ( $p=0.019$ , RR=2.53) had an independent significant influence on DFS. Univariate analysis for OS selected the following variables as unfavorable prognostic factors: CRP $>5$ , histological grade 3, age of patients  $>60$  years and non-adequate surgical margins. The patients with the levels of CRP  $>5$  mg/dl had significantly poorer prognosis than the patients with CRP values  $\leq 5$  mg/dl (40% three-year OS vs. 81% three-year OS). In multivariate analysis of OS, including all significant prognostic factors from univariate analysis of OS, CRP ( $p=0.005$ , RR=3.46), age of patients ( $p=0.008$ , RR=3.21) and adequate surgical margins ( $p=0.047$ , RR=2.68) retained a statistically significant independent prognostic impact.

**Conclusion:** Pre-treatment serum CRP is an independent prognostic factor for DFS and OS in patients with high-grade soft tissue sarcomas. The normal CRP group showed significantly more favorable prognosis than the elevated CRP group. In our poor risk patients with soft tissue sarcomas, CRP is even the strongest independent prognosticator of DFS and OS. Thus, CRP deserves further research helping us to classify patients with high grade soft tissue sarcomas into different prognostic subgroups more accurately. We need long term results for confirmation of CRP as an important prognostic factor in patients with soft tissue sarcomas on a large scale basis according to the rarity of this malignant disease.

Pohlig F.<sup>1</sup>, Kirchhoff C.<sup>1</sup>, Lenze U.<sup>1</sup>, Schauwecker J.<sup>1</sup>, Rechl H.<sup>1</sup>, von Eisenhart-Rothe R.<sup>1</sup>

<sup>1</sup> Department for Orthopaedic Surgery

Klinikum Rechts der Isar

Technische Universität München

Ismaningerstrasse 22 - 81675 Munich - Germany

**Objectives:** Biopsy in patients with suspected bone or soft tissue sarcoma represents one of the crucial steps in the diagnostic cascade. Open biopsy is still considered the gold standard. However, recent literature suggests similar results for percutaneous biopsy techniques. Therefore the aim of this retrospective study was to compare open and percutaneous core needle biopsy (CNB) in malignant musculoskeletal lesions.

**Materials and methods:** Overall 77 consecutive patients with a suspected malignant primary bone or soft tissue tumor who underwent a percutaneous CNB or open biopsy and a subsequent tumor resection in our department from January 2007 to December 2009 were identified and enrolled. The harvested samples were fixed in 10% formalin and routinely stained with H&E. Immunohistochemical stains were applied if appropriate. Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV) and diagnostic accuracy were calculated for both biopsy techniques and compared using the Fisher's exact test.

**Results:** Sensitivity, specificity, PPV, NPV and diagnostic accuracy were 100% for CNB in bone tumors. Sensitivity (95,5%) and NPV (91,7%) for open biopsy in bone tumors showed slightly inferior results without statistical significance ( $p=1$ ). In soft tissue tumors favorable results were obtained in open biopsies compared to CNB with differences regarding sensitivity (100% vs. 81,8%), NPV (100% vs. 50%) and diagnostic accuracy (100% vs. 84,6%) again without statistical significance ( $p>0,05$ ). Overall the diagnostic accuracy was 92,9% for CNB and 98% for open biopsy. A specific diagnosis could be obtained in 84,2% and 93,9% respectively ( $p=0,34$ ). Inferior results were identified for CNB in soft tissue tumors compared to bone tumors regarding sensitivity (81,8% vs. 100%,  $p=0,5$ ), NPV (50% vs. 100%,  $p=0,09$ ) and diagnostic accuracy (84,6% vs. 100%).

**Conclusions:** In our study moderately inferior results were found for the percutaneous biopsy technique compared to open biopsy in soft tissue tumors whereas almost equal results were obtained in bone tumors. Thus, CNB is a safe, minimal invasive and cost-effective technique for diagnostics of bony lesions. In soft tissue masses indication for percutaneous core needle biopsy needs to be set carefully by an experienced orthopedic oncologist with respect to suspected entity, size of necrosis and location to avoid incorrect or deficient results.

## CLINICAL VALUE OF PROLIFERATION AND APOPTOSIS MARKERS IN TUMOR CELLS IN OSTEOGENIC SARCOMA

078

*Djamila Sh.Polatova, Khurshid G.Abdikarimov, Sundr D.Urunbaev*

*National Oncology Research Centre, Tashkent, Uzbekistan*

**Aim:** To establish prognostic role of expressions of apoptosis and proliferation in osteogenic sarcoma.

**Materials and methods:** 46 patients till 30 have been examined, 30 - men and 16 - women ( $T_2N_{0-1}M_0$ ). Expressions of genes p53, Bcl-2 и Ki-67 in tumor cells have been studied by the method of immune histochemistry with monoclonal (Novocastra). Visualization have been executed with using Streptavidin – HRP and DAB (Dakocytomation).

**Results:** Organ-conserving operations have been performed in 16 patients (10 men, 6 women). Full effect and partial effect was marked in these patients, but expressions of genes mtp53 Ki-67 was low (1+) or absent. Expressions of genes bcl-2 was also low (1+). Crippling operations have been performed in 20 men and 10 women patients with osteogenic sarcoma, from them in 9 patients was detected metastasis further. Partial effect and stabilization of tumor process was marked in all patient of these group, but the expressions of genes mtp53 and Ki-67 was high and moderate (3+, 2+), but expression of genes bcl-2 was moderate (2+) and high (3+).

**Conclusion:** Definition the level of genes expressions mtp53, Ki-67 and bcl-2 in tumor cells, we can use conducted therapy for effective prognosis in the choice of osteogenic sarcoma treatment .

TG KASHIMA, A DONGRE, F PEZZELLA, NA ATHANASOU \*

Department of Pathology, NDORMS, University of Oxford, Nuffield Orthopaedic Centre, Oxford OX3 7HE

**OBJECTIVES:** aP2 (adipocyte P2), also known as FABP4 (fatty acid-binding protein-4) is a fatty acid binding protein found in the cytoplasm of cells of adipocyte differentiation. We and others have previously shown that immunohistochemistry with a polyclonal antibody to aP2 is useful in detecting lipoblasts. In this study we examined a large number of soft tissue tumours with a newly developed anti-aP2 monoclonal antibody to determine its utility in the diagnosis of tumours of adipose differentiation.

**MATERIALS & METHODS:** An anti-aP2 monoclonal antibody was raised against a mixture of synthetic peptides corresponding to the amino acid sequence of residues 10 - 28 and 121-132 of the human aP2 protein. Hybridoma-conditioned medium was tested for the production of anti-aP2 antibody by an enzyme-linked immunosorbent assay using the immunized synthetic peptides. Expression of aP2 was immunohistochemically determined using the selected supernatants in paraffin sections of normal adipose tissue and a wide range of benign and malignant primary soft tissue tumours (n=120)

**RESULTS:** Fat cells in normal adipose tissue and benign lipomas expressed aP2/FABP around cytoplasmic lipid vacuoles. Hibernomas and lipoblastomas showed strong aP2 staining of brown fat cells and lipoblasts respectively. Spindle cell lipomas showed positive staining of the fat but not the spindle cell component. Lipoblasts in atypical lipomatous tumour/well differentiated liposarcoma, sclerosing liposarcoma, myxoid/round cell liposarcoma and pleomorphic liposarcoma reacted strongly for aP2. No specific staining was seen in the tumour component of malignant tumours containing (lipoblast-like) clear or vacuolated cytoplasm including clear cell sarcoma, myxofibrosarcoma, leiomyosarcoma, alveolar soft part sarcoma and clear cell carcinoma. Capillary endothelial cells were positive for aP2 but fibroblasts, muscle and other cell types were negative.

**CONCLUSION:** The 175D (anti-aP2) antibody reacts with mature and immature fat cells. aP2 is expressed in tumours of adipose differentiation. aP2 expression is useful in identifying lipoblasts and should thus be useful in distinguishing liposarcoma from other sarcomas and malignancies which contain (lipoblast-like) tumour cells with a clear or vacuolated cytoplasm.

	Tumour type	number of cases	lipoblasts detected by IHC
ADIPOCYTIC TUMOUR	LIPOMA	16	0
	HIBERNOMA	3	3
	LIPOBLASTOMA	5	5
	SPINDLE CELL / PLEOMOPHIC LIPOMA	6	0
	ATYPICAL LIPOMATOUS TUMOUR / WELL DIFFERENTIATED LIPOSARCOMA	22	22
	SCLEROSING LIPOSARCOMA	3	3
	MYXOID LIPOSARCOMA	4	4
	ROUND CELL LIPOSARCOMA	4	4
	PLEOMORPHIC LIPOSARCOMA	4	4
	DEDIFFERENTIATED LIPOSARCOMA	2	0
TUMOURS SHOWING MYXOID CHANGE	MYXOMA	8	8
	MYXOFIBROSARCOMA	11	0
	SOLITARY FIBROUS TUMOUR / HAEMANGIOPERICYTOMA	3	0
OTHER SARCOMAS	LEIOMYOSARCOMA	4	0
	ALVEOLAR SOFT PART TUMOUR	1	0
TOTAL		96	

## THE IMPORTANCE OF 3D PLANNING: TUMOR RESECTION OF THE PROXIMAL RADIUS SPARING THE RADIAL HEAD.

089

K.Modaressi, L.Nagy, A.Schweizer, B.Fuchs

University Hospital Balgrist, Orthopedic Research, Forchstrasse 340, 8008 Zürich

**Introduction:** Sophisticated radiological imaging studies nowadays allow the precise delineation of a musculoskeletal tumor preoperatively. This in turn paves the way for precise resections accepting closer margins with respect to the tumor. Preoperative 3D planning and intraoperative navigation plays therefore an increasingly important role in tumor surgery. Herein, we report our experience with 3D planning for a patient in whom the proximal radius was resected but sparing the radial head.

**Results/Case Report:** Preoperative CT imaging was used to 3D-print a plastic radius model. Then, the resection margins were determined and a custom made titanium plate as well as a cutting block device including the drill holes were manufactured. The proximal resection margin was chosen that only 1.5cm of the radial head could be preserved. Intraoperatively, the tumor was exposed and the cutting device was mounted. The drill holes were prepared in the radial head such that after resection, it could be fixed in the correct 3D position as before. An allograft was carpentered to precisely fit into the defect, and then the custom made titanium plate was used to fix it.

**Conclusions:** 3D planning and the manufacturing of a custom made cutting/pre-drill device can be very helpful for tumor resections at anatomically difficult locations and when a remaining bone has to be precisely retained in its original anatomic position.



# IN VIVO MICRO-COMPUTED TOMOGRAPHY CAN VISUALIZE AND QUANTIFY OSTEOSARCOMA PRIMARY TUMOR GROWTH AND PULMONARY METASTASES OVER TIME.

090

S. Botter, K. Husmann, M. Arlt, C. Campanile, A. Gvozdenovic, W. Born, B. Fuchs

University Hospital Balgrist, Orthopedic Research, Forchstrasse 340, 8008 Zürich

**Introduction:** In osteosarcoma (OS), one important imaging tool to assess the extent of primary tumor growth, metastatic spread (mainly in the patients' lungs), and thus patient prognosis is computed tomography (CT). In the past two decades, this technique has been adapted in order to image small laboratory animals like mice. As such, micro-CT imaging proved its functionality in a number of other cancer types. In our laboratory, we established a method to visualize the presence of single OS tumor cells *ex vivo*, by means of LacZ tagging. However, what exactly occurs during the course of the disease process remains largely unknown, since *in vivo* visualization methods are not yet commonly employed in preclinical OS models. We therefore tested if *in vivo* micro-CT can be employed to monitor the growth of both the primary tumor as well as the pulmonary metastases in a preclinical OS model.

**Methods:** Female SCID mice received an intratibial injection with LacZ-tagged osteoblastic SAOS-2 or osteolytic 143B OS cells. After growth of the primary tumor, mice were anesthetized and scanned in the Skyscan 1176 *in vivo* microtomography system using the 35  $\mu\text{m}$  setting. Two separate scans were made, one of the chest area and one of the hind limbs. Scan duration per scan was 8-10 minutes, with a dose of  $\sim 0.5$  Gy. After two weeks, the scans were repeated. As verification, mice were sacrificed immediately after the second scan, and their lungs were excised, X-Gal stained, air-dried, and scanned again at high (9  $\mu\text{m}$ ) resolution.

**Results:** In mice injected with SAOS-2 cells, mineralized foci could be observed inside the primary tumor mass, as well as in the pulmonary metastases. The size of the smallest detectable metastasis was 0.5 mm. In the second scan, the mineralized foci became more pronounced. In 143B tumors, bone destruction at the proximal tibia could be visualized in detail. X-Gal stained and re-scanned lungs showed a perfect match between X-Gal staining and micro-CT-detected metastatic sites *ex vivo*.

**Conclusions:** Micro-computed tomography can be used to monitor both primary and distal OS tumor growth *in vivo*, and reveals detailed 3D information of micro-metastasis distribution *ex vivo*. Future challenges will be to increase the contrast between tumor tissue and normal tissues, e.g. by using gold-labeled antibodies directed against specific tumor markers, and thus to be able to identify and monitor even smaller metastases over time.

# CD44 OVEREXPRESSION ENHANCES METASTATIC PROPERTIES OF HUMAN OSTEOSARCOMA SAOS-2 CELLS IN VITRO AND IN VIVO

091

A. Gvozdenovic, M. Arlt, C. Campanile, P. Brennecke, W. Born, R. Muff, B. Fuchs

University Hospital Balgrist, Orthopedic Research, Forchstrasse 340, 8008 Zürich

**Introduction:** Pulmonary metastases are the major cause of death in patients suffering from OS, a disease mainly affecting children and adolescents. At the time of diagnosis, up to 15-20% of patients already have detectable metastases. Patients with metastatic or recurrent disease continue to have a poor prognosis, with a 5-year survival rate of 10-20%. Thus, it is of substantial importance to identify molecular markers in OS associated with increased metastatic potential. CD44 is frequently found overexpressed in tumour cells and has been implicated in metastasis of different cancer types. It is a cell-cell and cell-matrix adhesion molecule and the principal receptor for hyaluronan (HA), a major component of the extracellular matrix. CD44 has a wide repertoire of functions in biological processes, including development, wound healing, inflammation, haematopoiesis, immune response and tumor progression. Here, we investigated the effects of stable CD44 overexpression on in-vitro and in-vivo metastatic properties of low metastatic human LacZ-transduced SaOS-2 (SaOS-2/LacZ) OS cells expressing low levels of endogenous CD44.

**Methods:** To assess the relevance of CD44-HA interaction in promoting metastatic ability of OS cells, we overexpressed both, the standard CD44 isoform CD44s and the HA binding-defective mutant CD44s R41A in SaOS-2/LacZ cells using retroviral gene transfer. Overexpression was examined on Western blots. The biological impact of CD44s and CD44s R41A overexpression was then studied in-vitro in adhesion, transwell migration and proliferation assays. Effects of CD44s and mutant overexpression on tumor progression and metastasis in-vivo were investigated in an intratibial xenograft OS model in SCID mice.

**Results:** SaOS-2/LacZ cells overexpressing CD44s showed increased adhesion to HA, whereas overexpression of binding-defective CD44s R41A did not affect the adhesion when compared to empty vector (EV) transduced SaOS-2/LacZ control cells. Overexpression of CD44s and CD44s R41A resulted in HA-independent higher migration rates. In the orthotopic mouse model of OS, CD44s overexpression led to faster primary tumor growth and increased numbers of micro- and macrometastases in the lungs in a HA-dependent manner.

**Conclusions:** These results highlight the important role of CD44/HA interaction in determining tumor malignancy in experimental OS in mice.

Campanile C<sup>1</sup>, Arlt M<sup>1</sup>, Honer M<sup>2</sup>, Kraemer SD<sup>2</sup>, Ametamey SM<sup>2</sup>, Schibli R<sup>2</sup>, Born W<sup>1</sup>, Fuchs B<sup>1</sup>

<sup>1</sup>University Hospital Balgrist, Orthopedic Research, Zurich

<sup>2</sup>Institute of Pharmaceutical Sciences, ETH Zürich

**INTRODUCTION:** Osteosarcoma (OS) is the most common malignant bone tumor in children and adolescents characterized by the production of immature bone, osteoid. In normal bone, the resorption by osteoclasts is linked to bone formation. In OS, osteolytic and osteoblastic phenotypes, as a result of imbalanced bone resorption and formation, are distinguished radio- and histologically. The different phenotypes, associated with differences in tumor proliferation and hypoxia, determine at least in part the response to chemotherapy and, consequently, the patient's outcome. Novel minimally-invasive diagnostic tools are needed for future more patient-tailored treatment depending on more precisely defined tumor phenotypes. Here, Positron Emission Tomography (PET) with <sup>18</sup>F-FDG, indicating glucose metabolism, <sup>18</sup>F-Fluoride, indicating bone remodelling and <sup>18</sup>F-FMISO indicating hypoxia, is used in 3 different mouse models with well-defined phenotypes, reflecting OS heterogeneity, to evaluate the respective predictive power of the 3 PET tracers in OS diagnostics.

**METHODS:** 2 human (143B, osteolytic; and SaOS-2, osteoblastic) and 1 mouse OS cell line (LM8-osteoblastic) were intratibially injected in SCID immunosuppressed and C3H immunocompetent mice, respectively. Intratibial primary tumor development was monitored by X-ray. PET was performed at the Animal Imaging Center at ETH-Hönggerberg 3 weeks after tumor cell injection in the 143B and LM8 models and between 2 and 5 months after injection of human SaOS-2 cells in SCID mice. Tracer uptake in the tumor leg was quantified with p-mod software and compared to the control leg.

**RESULTS:** In the 143B cell line, a significantly higher uptake of FDG and FMISO is observed in the tumor compared to the control leg, but there is no difference in Fluoride uptake which is consistent with the histological results. The SaOS-2 cell derived tumors, on the other hand, display high uptake of FDG, FMISO and Fluoride, reflecting a proliferative and hypoxic osteoblastic phenotype. LM8 mouse OS cell derived tumors show a high tumor selective accumulation of FDG, but only moderate uptake of FMISO and Fluoride consistent with low osteoblastic activity and hypoxia.

**CONCLUSIONS:** FDG, FMISO and Fluoride proved to be predictive in the 3 intratibial OS mouse models with well characterized phenotypes and therefore suitable for primary tumor monitoring in pre-clinical studies investigating novel phenotype- and histotype-specific treatment modalities.

# EFFECTIVENESS OF ULTRASOUND INVESTIGATION IN THE DIAGNOSIS AND PREDICTION OF EVENT-FREE SURVIVAL IN PATIENTS WITH BONE SARCOMAS

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I. Begun<sup>1,2</sup>, I. Papkevich<sup>1</sup>, R. Tarasevich<sup>1</sup>, O. Bydanov<sup>1</sup>, A. Mikhailov<sup>2</sup>

<sup>1</sup>. Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk region, Belarus

<sup>2</sup>. Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus

**Purpose:** Study the effectiveness of ultrasound for diagnoses and prognostic significance of Doppler pulsatility index (PI) for common femoral artery (CFA) in patients with osteogenic sarcoma (OS) and Ewing's sarcoma (SE).

**Material and Methods:** We analyzed data of integrated ultrasound investigation in 47 children and adolescents aged 7-17 years with prospectively confirmed diagnosis of osteogenic sarcoma (27) and Ewing's sarcoma (20). In all cases process was localized in the tubular bones of the lower extremities. In Comparison group were 42 children of similar age with benign tumors and tumor-like conditions (osteoid osteoma, cyst, fibrous dysplasia, osteochondroma, calcified hematoma, venous dysplasia). When evaluating the diagnostic indicators we used mathematical apparatus of ROC analysis. Data are presented as the values of percentage deviations of resistive index (RI%), pulsatility index (PI%) and volumetric blood flow velocity (Q%) in the common femoral artery (CFA) of the affected limb compared with the contralateral. Patients with SE and OS received chemotherapy according to protocols EURO-EWING-99 and COSS-96, EURAMOS respectively. We investigated too the prognostic significance of PI% for event-free five-year survival (EFS). Analysis was by Kaplan-Meier.

**Results:** Predominance of the size of the affected area of malignant neoplasms compared with benign noted. The average volume of tumor was  $257 \pm 244 \text{ cm}^3$ . The soft-tissue component of bone sarcomas was presented as heterogeneous echostructure. It was adjacent to the bone with altered in varying degrees of cortical integrity. The common features of malignant bone tumors in most cases were: irregular shape, fuzzy contours, low acoustic density, heterogeneity of echostructure. In 32% of patients were determined ultrasound signs of X-ray analogues periosteal reaction. In 80% - the degree of tumor vascularization was high and average. The cited symptoms above are allowed to help qualitatively differentiate between benign and malignant neoplasms. The efficiency of diagnosis has been increased with the use of quantitative data of triplex ultrasound scanning. We noted an increase in the volume velocity of blood flow in CFA for the affected limb and a decrease in RI and PI for CFA compared with the contralateral side ( $p < 0.01$ ), which could indicate a decrease in resistance for the distal circulatory bed on the side of the tumor. Analysis of quantitative data showed that the sensitivity and specificity in the differential diagnosis of sarcomas and benign tumors of bone of the lower limbs by criterion of reducing PI%, RI% and increasing of Q% (at threshold values - 23%, 10% and 15% respectively) were 79-96%.

For studying event-free survival cut-off value of the predictor PI% were selected that so information content of data analysis was maximal. For patients of all groups (OS, SE, OS+SE) best statistical representativeness of forecast EFS five-year for PI% were obtained when it's a threshold value there was 33%. Percentages of values deviation (downward) of PI for the affected limb were associated with 100% EFS in the event of occurrence in the range 33% and less, or with the EFS of  $26 \pm 7\%$  in case of entry into a range of more than 33% ( $p < 0.01$ ).

**Conclusions:** By multi modalities ultrasound were obtained by quantitative and qualitative characteristics bone sarcomas in children and adolescents. Comparative analysis of quantitative characteristics proximal blood flow in both healthy and the affected limb helps effectively distinguish between sarcomas and benign tumors of bones. It is established that the relative magnitude of the PI, characterizing changes in hemodynamic of affected limb, and, consequently, to a certain extent its supply blood, is associate with predicting EFS five- year in patients with bone sarcomas. Thus, relative changes of the Doppler pulsatility index in femoral artery of affected limb is opening a new features for prediction of event-free survival in patients with bone sarcomas.

# WHAT IS A SAFE SKIN MARGIN FOR THE RE-EXCISION OF INADVERTENTLY EXCISED SUPERFICIAL SOFT TISSUE SARCOMAS? A CLINICO-PATHOLOGIC STUDY

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CL Gaston, VP Sumathi, RJ Grimer

Royal Orthopaedic Hospital Birmingham, UK

**Introduction:** Superficial soft tissue sarcomas (SSTS) treated by previous inadvertent surgery require re-excision of the surgical bed for local control of residual and recurrent tumour. Recommended excision margins in literature range from 1, 2, or 3-5 centimeters. This study aimed to determine the effect of different skin excision margins on final surgical margin and outcomes (local recurrence, adjuvant treatment)

**Methods:** A retrospective review was done for the 115 patients with superficial STS treated at our institution after inadvertent excision from August 2004 – Dec 2011. Photographs of the resection specimens were analysed to determine the narrowest skin margin circumferentially from the previous surgical scar. This was correlated with the resulting surgical margin, need for adjuvant therapy, and local recurrence.

**Results:** The average skin margin for re-excision was 16.1 mm (range 4 – 30mm). Residual tumour was found in 56%. Skin margins were significantly narrower in patients with inadequate circumferential margins (12.6 vs 21.5mm,  $p < 0.001$ ). 84% of those with inadequate circumferential margins were excised with a skin margin of less than 2cm, 92% were excised with less than 3cm. Using 3cm skin margin as a cut-off was significantly associated with the need for further treatment (re-excision, adjuvant radiotherapy). No association to local recurrence was found. Six of 9 patients (67%) with myxofibrosarcomas were excised with inadequate circumferential margins despite the majority being excised with at least 2cm skin margins.

**Conclusions:** Narrow skin margins in re-excising the surgical scars of inadvertently excised superficial soft tissue sarcomas are associated with inadequate circumferential margins and consequently to further treatment with wider re-excision and/or adjuvant radiotherapy. We recommend that re-excision be made with at least a 3cm margin even without gross residual tumour to help prevent inadequate margins.

## DIAGNOSTIC PERFORMANCE OF TRUCUT BIOPSY IN MUSCULOSKELETAL TUMOURS

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Pedro Cardoso, Daniel Carquejo, Vânia Oliveira

Hospital Santo António – Porto - Portugal

**Objectives:** Currently, percutaneous needle biopsy is a diagnostic method widely used and well accepted, minimally invasive, safe and cost-effectiveness. Requires only local anesthesia and has reduced risk of complications and is becoming the preferred technique for diagnosing musculoskeletal lesions. The purpose of this study was to analyze the diagnostic performance of percutaneous core needle biopsy in musculoskeletal lesions in our Unit and whether this was influenced by the gauge of the needle used.

**Materials and methods:** it was performed a retrospective review of 142 cases of musculoskeletal lesions undergoing percutaneous core needle biopsy aided by imaging over a period of four years (January 2007 to December 2010). 122 biopsies corresponded to lesions of bone (65 cases with 11 gauge needle and 57 with 8 gauge needle) and 20 to soft tissue lesions (needle gauge 16). The diagnostic accuracy and diagnostic yield were the parameters used to evaluate the diagnostic performance.

**Results:** The overall diagnostic yield was 90.1% and diagnostic accuracy was 90.9%. In the pelvic biopsies diagnostic yield (77.1%) was significantly lower ( $p = 0.006$ ) as compared to other anatomical sites (94.4%). The diagnostic yield was 89.3% in bone and 95% in soft tissue ( $p = 0.381$ ), and diagnostic accuracy was 93.3% in bone lesions and 85.7% in soft tissue injuries ( $p = 0.379$ ). The diagnostic yield ( $p = 0.965$ ) and diagnostic accuracy ( $p = 0.313$ ) were not significantly different between the 11 gauge needle (89.2% and 88.2%, respectively) and 8 gauge needle (89.5% and 100%, respectively).

**Conclusion:** This study demonstrates that percutaneous core needle biopsy is useful and important as a diagnostic procedure in musculoskeletal disorders, and the results obtained in this institution are comparable or slightly better than other studies.

Rahim R. Abdurasulov<sup>1</sup>, Mirza A. Gafur-Akhunov<sup>1</sup>, Khurshid G. Abdikarimov<sup>2</sup>

<sup>1</sup>The Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan

<sup>2</sup> National Oncology Research Centre, Tashkent, Uzbekistan

**Background:** to study clinical manifestations and properties of pulmonary metastating process of osteosarcoma (OS).

**Material and methods:** we had analyzed 33 patients with OS pulmonary metastasis, which had been treated in the Republic Oncology Scientific Center of Uzbekistan, during 2007-2010 years. Female - 19 (58%), male – 14 (42%). Patients ages from 14 to 38 years, median age – 17. From 33 patients in 20 (60.6%) primary tumor localized in distal femur, in 8 (24.2%) – proximal tibia and in 5 (15.2%) – different parts of fibula. In 30 patients from 33 lung metastases were detected by x-ray examination and in 3 patients by computer tomography (CT).

**Results:** bilateral metastatic lesions of lungs detected in 20 (60.6%) and unilateral in 13 (in 6 (9.4%) – upper lobe of left lung, in 4 (12.4%) – lower lobe of right lung and in 3 (12.1%) – upper lobe of right lung) patients. Of the 33 patients in 31 (94%) lung metastases developed during from 1 to 24 months follow up, and in 2 (6%) at diagnosis of primary tumor. The numbers of metastatic nodules were 1-7, middle 2 nodules. Lung metastases were single in 9 (27.2%) and multiple in 24 (72.8%) patients. Metastatic nodules sizes in detected time were from 5mm to 25 mm, median 14.3 mm. Of 33 patients in 4 after lungs x-ray examination were carry out CT examination, so were detected additional metastatic nodules and difference in nodules size.

**Conclusions:** the target organ of OS metastatic spread is the lungs and in most cases had affected both lungs. Properties of metastatic OS is multiple affecting of the lungs.



## DOES A PREVIOUS INADVERTENT EXCISION AFFECT OUTCOME IN SUPERFICIAL SOFT TISSUE SARCOMAS?

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Rob Grimer and Lee Jeys

Superficial soft tissue sarcomas (STS) represent approximately 25% of all STS and about 50% have a previous inadvertent excision. We have investigated whether a previous inadvertent excision affects outcome.

**Method:** A retrospective review of a prospective database has been carried out. Only patients with treatment and follow up at our centre are included.

**Results:** there were 525 patients with a mean age of 55. The average size of the STS was 6cm. The most common site was the thigh, 83% were high grade. 281 patients (54%) had undergone a previous inadvertent excision and the others were treated primarily at our unit. The patients with previous excision had significantly smaller tumours (4.8cm vs 7.4cm.,  $p<0.0001$ ) and patients with DFSP or leiomyosarcoma were more likely to be diagnosed in this way. Most patients (400) underwent attempted wide re-excision with skin graft if primary closure could not be obtained (100). Wide margins were achieved in 60%, marginal in 33% and intralesional in 7%. Local recurrence arose in 16% of patients and was related to margins of excision, grade and age of the patient whilst overall survival was related to grade, age and size of the tumour. Previous inadvertent excision did not affect either LR or survival.

**Conclusion:** Having a previous inadvertent excision has no affect on either local recurrence or overall survival. Wide excision gives the best chance of local control. The very large size of these STS at diagnosis is a cause for great concern and undoubtedly worsens overall survival.

Pathologists are usually considered to be the arbiters of defining what margin has been achieved following resection of a sarcoma. Surgeons are usually thought to be too optimistic and will usually state ‘excised with clear margins’ when a pathologist will find the tumour is closer than anticipated. This study sets out to find who is better by comparing margins and outcomes in terms of local recurrence.

**Method:** 1208 patients with a variety of bone and soft tissue sarcomas had their margins of excision prospectively assessed by the surgeon immediately following the operation and an opinion on the actual margin was then given by the pathologist. The Enneking system of intralesional, marginal and wide was used. Outcomes were assessed using the rate of local recurrence split by margin type, highlighting differences between pathologists and surgeons.

**Results:** 1208 patients had an assessment of margins by both surgeon and pathologist. Of these there was agreement in 984. In the other 224 cases the surgeon felt he had a worse margin than the pathologist in 112 and the pathologist worse than the surgeon in 112. The crude local recurrence rates are shown in the table below:

Status	Number	Crude LR rate
Agreed intralesional	276	35%
Surgeon intralesional, pathol marginal	21	45%
Pathol intralesional, surgeon marginal	36	29%
Agreed marginal	143	23%
Surgeon marginal, pathol wide	58	21%
Pathol marginal, surgeon wide	51	16%
Agreed wide	335	11%

**Discussion:** These results show that surgeons are in fact more realistic about their margins than might be expected. If they state that they have an intralesional or a marginal margin then the local recurrence rates will be higher than if they both agree. If the pathologist says a margin is closer than the surgeon thinks it is then the LR rate is not as bad as if the surgeon is worried.

**Conclusion:** Surgeons opinions on margins are important and can add value to a pathologists report. Taking the worse of the two values as the agreed margin would seem to make sense!

# SERUM ALKALINE PHOSPHATASE AND LACTIC DEHYDROGENASE – PROGNOSTIC SIGNIFICANCE IN TREATMENT OF CHILDHOOD OSTEOSARCOMA

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Bekic Z<sup>1</sup>, Ilic V<sup>1</sup>, Lujic N<sup>2</sup>, Vucinic Z<sup>2</sup>, Pudrlja-Slovic M<sup>1</sup>

<sup>1</sup>Institute for Oncology and Radiology of Serbia, Belgrade;

<sup>2</sup>Institute for Orthopedic Surgery Banjica, Belgrade, Serbia

**Aim:** The aim of the study was to evaluate the value of serum alkaline phosphatase (SALP) and lactic dehydrogenase (SLDH) in children with nonmetastatic osteosarcoma (OS).

**Methods:** From 1988-2003, we treated 123 patients with classic high-grade OS, median age 15 years (range 3-18). The majority of patients (80%) had tumor in the region of the knee joint. At the moment of diagnosis, the level of SALP was increased in 51 pts (41%) and SLDH in 32 pts (26%).

Adjuvant chemotherapy after amputation was administered in 32 pts. Neoadjuvant chemotherapy was administered in 91pts followed by surgery (amputation, rotatinoplasty or tumor resection). Tumor necrosis over 90% was found in 43 pts. Chemotherapy regimens were administered in all patients (Adr/CDDP, T-10, COSS 96).

**Results:** During the 18 - 238 months follow up period, overall survival (OS) rate after 5, 10 and 15 years was 61%, 50% and 47%, respectively.

In the group of pts with initially elevated SALP level, the survival rate was significantly lower than in the group with the normal SALP level ( $p<0.01$ ). Survival rate was also significantly lower in the group of pts with initially elevated SLDH than in the group with normal level ( $p=0.026$ ).

**Conclusion:** The prognostic significance of SALP and SLDH are still controversial. However, in our study, they had significant prognostic value and might be used, in correlation with other parameters, to stratify patients in new clinical trials.

Perisano C, Graci C, Spinelli MS, Del Bravo V, Valenzi E, Di Giacomo G, Fabbriani C, Maccauro G.

Department of Orthopaedics and Traumatology, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart School of Medicine, Rome, Italy

**Objective:** Deep venous thrombosis (DVT) mainly affects the large veins in the lower leg and thigh and is one of the most prevalent medical problems today, with an annual incidence of 80 cases per 100,000. On the contrary soft tissue sarcomas are rare tumors, with an estimated incidence averaging 4/100 000/year in Europe. Tumors in the hip or thigh may be associated with a particularly high risk of thromboembolism. The aim of the study is to analyze as the DVT or pulmonary embolism may be a pitfall in the early diagnosis of soft tissue sarcoma of the lower limb because the rarity of these lesions and the imaging may not initially reveal a sarcoma as the cause for DVT.

**Material and Methods:** The authors report two clinical cases of a 47 years old man who presented a DVT of the right lower extremity, managed conventionally with oral anticoagulant and the case of a 42 years old women who presented a pulmonary embolism . Physical examination and ultrasound didn't reveal a tumor but only the signs of DVT. Both were treated for DVT for 8 and 4 months respectively. In view of persistent symptoms and inefficacy anticoagulant therapy, magnetic resonance imaging and biopsy were undertaken to uncover the underlying pathology.

**Results:** Imaging and biopsy revealed in the first case a leiomyosarcoma, adherent to the femoral vein, in the second case a MFH localized in thigh closed to the femoral vein that were the cause of persistent symptoms despite anticoagulation, possibly by its local mass effect and also by its potential to create a thrombogenic milieu; Excision of the tumor followed by chemotherapy and radiotherapy in the first case and by brachithery and radiotherapy in the second case, led to symptom regression and at 2 years of follow-up the patients are free from disease.

**Conclusion:** Vascular leiomyosarcoma or Soft tissue sarcomas can present or mimic or be misdiagnosed with the DVT. This two cases want to highlight the importance of considering neo-plastic masses as differential in painful leg swelling. Diagnosis is made with MRI. Treatment involves surgical excision that provides symptom relief as well as avoids potential tumour extension. A delay of diagnosis and treatment of sarcoma may result in the poor prognosis in tumor with survival rates if treated early ranged from 73% to 79% at 5 years; it is important that all physicians know that soft tissue sarcoma can present initially as DVT in particular in younger patients and in those with recurrent or refractory thrombosis or symptoms.

# PREGNANCY AT THE TIME OF DIAGNOSIS OF BONE SARCOMAS

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Bartoli MS<sup>1</sup>, Gaston CL<sup>2</sup>, Grimer RJ<sup>2</sup>

<sup>1</sup>*Scuola di Specializzazione in Ortopedia e Traumatologia, Università degli Studi di Milano, Italy* <sup>2</sup>*Orthopaedic Oncology Unit, Royal Orthopaedic Hospital, Birmingham, UK*

**Introduction:** Women who are pregnant at the time of diagnosis of a primary malignant bone tumour pose significant challenges in terms of treatment both of the pregnancy and the tumour. There is a perception that they may do worse than other patients because of this. We have evaluated our unit's experience of this.

**Method:** Retrospective review of a prospectively collected database.

**Results:** 20 patients developed a bone tumour while they were pregnant. Their mean age was 28 (range 17 to 39). There were 6 osteosarcomas, 7 chondrosarcomas, 2 Ewings, 4 spindle cell sarcomas and 1 giant-cell rich high grade sarcoma. The most common site was the pelvis followed by the distal femur. Tumours were diagnosed during pregnancy in 10 out of 20 patients. Three women were in their first trimester, 2nd trimester in 6 patients, and 1 was in 3rd trimester. The other 10 patients developed symptoms related to the tumour during pregnancy, but histologic diagnosis was made 2 days to 6 months after delivery. Of the 9 patients who underwent chemotherapy, 3 had terminations and 2 had premature induction of labour. Limb salvage was done in 17 (85%) but 3 (15%) needed an amputation. 5 had surgery whilst pregnant and there were no adverse outcomes from this. Survival was 86% at 2 years and 59% at 5 years but this decreased to 75% and 50% respectively in patients who needed chemotherapy. Local recurrence arose in 3 (15%) and lung metastasis in 5 (25%). One of the newborns developed acute meningitis and died within the first month. There were no other adverse events among the other 16 neonates.

**Conclusions:** Fortunately primary bone sarcomas arising in pregnancy are rare. There are often difficult decisions to be made about treatment especially when chemotherapy is needed. Diagnosis and treatment was often delayed until after pregnancy and this along with common pelvic involvement, accounts for those with bad outcomes. In patients whom treatment was not delayed, survival rates were comparable. A multidisciplinary approach, including oncologist, radiologist, orthopaedic surgeon, psychologist, and gynaecologist is mandatory.

Daniel Soares, Vânia Oliveira, Luciana Leite, Luís Costa, Pedro Leite, Pedro Cardoso

Department of Orthopaedics

Centro Hospitalar do Porto – Hospital Geral de Santo António - Oporto, Portugal - [www.chporto.pt](http://www.chporto.pt)

**Introduction and Objectives:** In orthopaedic oncology it is clear-cut that diagnosis should be based on history, clinical and imaging data, both macroscopic and histological.

However, it is not infrequent to be confronted with inadequate conducts of irreparable consequences, such as excision biopsies of “benign tumours”, of which histological diagnosis confirms malignancy, demanding large or radical excisions. Similarly, there are some metabolic and reactive lesions that can mimic bone neoplasms but should be recognised after anamnesis and imaging, without need, sometimes, for biopsy.

This revision pretends to stress the importance of an accurate evaluation in orthopaedic oncology, therefore avoiding unnecessary exams and allowing opportune and adequate therapeutic choices.

**Material and Methods:** In order to emphasise the importance and to contribute to improvement in clinical approach and management, the authors present an interesting collection of cases and imaging documentation of non-neoplastic pathologies simulating bone neoplasies: myositis ossificans, myositis ossificans progressiva, reactive lesions of the bone surface (florid reactive periostitis, Nora’s lesion, subungueal exostosis), exuberant fracture callus, avulsion and stress injuries, posttraumatic and pubic osteolysis, tumoral calcinosis, tophaceous gout and pseudogout, chronic recurrent multifocal osteomyelitis, hyperparathyroidism brown cells’ tumour, amyloidosis of bone.

All the cases presented were studied, diagnosed and treated at the musculoskeletal tumors unity of the Orthopaedics Department of Centro Hospitalar do Porto.

**Discussion and Conclusion:** There are several non-neoplastic pathologies that can simulate bone neoplasies and should, therefore, be kept in mind by every orthopaedic surgeon. The collection presented by the authors serves as a complete and systematised compilation of these conditions

*T. Perlaky, K. Szurián, Z. Sápi, M. Szendrői*

*Semmelweis University, Department of Orthopedics*

*Semmelweis University, I. Department of Pathology*

*Budapest, Hungary*

**Objectives:** A precise histological diagnosis is fundamental in the treatment of soft tissue tumors. The gold standard and the most reliable method is incisional biopsy. Although it gives an almost 100% accurate result, it comes along with a relatively high risk of tumor contamination – an unwanted side effect of the diagnostic algorithm. Aspiration cytology is an easy way of obtaining a diagnose, however its accuracy and sensitivity is sometimes questioned. In the present study, malignant soft tissue sarcoma cases of our department were evaluated to define the diagnostic accuracy of aspiration cytology.

**Materials and methods:** 480 soft tissue sarcoma cases have been evaluated for the study, that have been treated at our department in the past 15 years. The cases with previous aspiration cytology had been selected, then preoperative diagnose was compared to the final diagnose given by the histological examination of the excised tumor.

**Results:** Aspiration cytology has been performed in 43% of all malignant cases. The findings were divided into four groups by the opinion of the pathologist: I.: benign, II.: malignant without diagnosis, III.: tumor of questionable nature and IV.: malignant with exact diagnosis. All the false negative cases were enrolled into the I. group, that covered 8 % of all cases. The II. and IV. groups referred to the sensitivity of the procedure, which achieved 84 %. The III. group extended 8 % of the cases. In this group of patients the nature of the tumor was determined by the help of imaging examinations or by other biopsy methods.

**Conclusions:** Open biopsy is still the gold standard in the diagnostic algorithm of soft tissue sarcomas. Aspiration cytology with combined cytopathology and ancillary techniques, like fluorescence in situ hybridization (FISH), DNA cytometry, and immunocytochemistry is almost as effective and reliable as incisional biopsy. For the best results, the cooperation of an experienced pathologist and the surgeon is essential. According to this study, we recommend aspiration cytology for preoperative, minimal invasive diagnostic step in the treatment of soft tissue sarcomas.



Martynkov DV, Kondratjeva TT, Kharatishvili TK, Aliev MD

FGBU N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences

Moscow, Russian Federation

**Objective:** To analyze approaches to the cytological diagnostic of recurrence of STS.

**Materials and methods:** We analysed 174 patients treated in RCRC RAMS in 2000-2010 years with recurrent soft tissue sarcomas. 96 (55,2%) of patients performed cytologic evidence of tumor by puncture with fine needle. Among these patients were 46 (47,9%) male and 50 (52,1%) female. Mean age years  $43,8 \pm 14,2$  (range 18-77). Histological type of the primary tumor was: MFH – 28,1%, synovial sarcoma – 17,7%, liposarcoma – 21,9%, malignant peripheral nerve sheath tumors – 18,8%, leiomyosarcoma – 7,3%, etc. Fine needle aspiration cytology (FNAC) under ultrasound guide was performed once in 76 cases (79,2%), twice in 6 cases (6,3%), three times – 14 cases (14,6%). Scar structure made it difficult to visualize the tumor.

**Results:** Cytological evidence of tumor was obtained in 84/96 (87,5%) of cases. Other 12 samples were unhelpful. Diagnosis of malignant lesion was in 78/96 (81,3%) cases. Diagnosis of soft tissue sarcoma – in 64/96 (66,7%) cases. Of the sarcoma aspirates, 28/64 (43,8%) could be subtyped. FNA diagnosis was confirmed histologically in all cases.

**Conclusions:** The cytological examination is necessary to confirm the recurrent process for further treatment, especially in cases where amputation is needed. A cytopathologic diagnosis of malignant lesion was found in 78/96 cases (81,3%). A FNAC is useful and accurate method in the detection of local recurrences of soft tissue sarcomas.

# ULTRA SOUND GUIDED CORE NEEDLE BIOPSY OF SOFT TISSUE MASSES: AN INTERDISCIPLINARY PROCEDURE.

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Simona Pozza, Armanda De Marchi, Paola De Petro, Federica Gunetti, \*Alessandra Linari, \*\*Elena Brach del Prever, \*\*\*Raimondo Piana, \*\*\*Gian Carlo Gino, Carlo Faletti.

Department of Radiology, AO CTO/Maria Adelaide of Turin, Italy

\*Department of Pathology, AO OIRM-S. Anna of Turin, Italy

\*\*Department of Traumatology, Orthopaedics and Health Medicine, University of Turin, Italy

\*\*\*Department of Oncological Orthopaedics and Reconstructive Surgery, AO CTO/Maria Adelaide of Turin, Italy

**Background and aim:** Diagnosis of soft tissue masses can be a difficult, long and expensive procedure. Biopsy is the last diagnostic step and can be an "hazard": if the tissue sample is not representative for quality and/or quantity, biopsy can conduct to a wrong or delayed diagnosis; if the approach is not correct, biopsy can contaminate the surrounding tissue and compartments, with consequences on surgical resection till impossibility of limb salvage. Core needle biopsy (CNB) can be a good diagnostic technique if ultrasound (US) guided and after a correct and planned interdisciplinary diagnostic strategy. Aim of this work is to evaluate the adequacy, sensibility and specificity of US guided CNB performed after Contrast Enhancement study (CEUS) in soft tissue masses of limbs and trunk.

**Materials and Methods:** In the last ten years more than 1200 US guided CNBs of soft tissue masses were performed at CTO Hospital in Turin, Regional Referral Center for Bone and Soft Tissue Sarcoma (STS). The strategy for diagnosis is interdisciplinary, coordinated by the orthopaedic surgeon, who will perform eventually the surgical procedure. Standard US study is completed by Power Doppler and CEUS. The contrast medium consists of micro-bubbles filled with sulphur hexafluoride (SonoVue® Bracco, Milan, Italy), evaluated by a low Mechanical Index dedicated devices. All patients are informed and give their informed consent. When necessary, Ethic Committee is informed and gives its authorisation. CNB is performed focusing the needle in the area with more anarchic vascular supply, typical of tumoral neangiogenesis; necrotic and hemorrhagic area are easily identified and not sampled in order to improve the quality and adequacy of the samples. At least two-three samples are obtained with two-three CNB. All biopsies are performed using the same "surgical approach" as for definitive oncological en-bloc surgical resection: in this way the surgeon can resect the biopsical tract en bloc with the tumour. The correct procedure was obtained, at the beginning, with a "joint contemporary interdisciplinary technique": the radiologists studied by CEUS and identified the more representative area; the orthopaedic surgeons showed the correct approach; the pathologist controlled the quality of samples. With time and experience, now the radiologists alone perform the US guided CNB after discussion of the case at the interdisciplinary meeting, when hypothesis on histology and surgical definitive procedure are advanced according to clinical history, physical exam, imaging.

**Technique of US guided CNB after CEUS study:** Cutaneous or local-regional anesthesia are not necessary: a detailed explanation of the procedure has allowed us in all cases to obtain full cooperation from patients. The procedure is conducted with sterile methods: accurate disinfection of the skin, two medical operators with sterile gloves. The ultrasound probe is covered with a sterile plastic cover; a dedicated device is used to focus the biopsy (Mylab®, Esaote, Genova, Italy). Needles usually are 14 or 16 G... Two-three samples are obtained: their macroscopic quality is controlled before to place them in a sterile container with 4% formaldehyde; they are sent within 3 hours to the pathology laboratory. The CNB is focused in areas highlighted by CEUS, using the same approach as for an eventually definitive surgical treatment, respecting anatomical compartments. After the procedure, the patient rest for one hour with local ice. US is performed after at least one hour in order to exclude bleeding.

**Results:** No major complications occurred; no disseminations along the needle track were observed. No modification for surgery occurred due to CNB. Our procedure allowed us to achieve excellent results in terms of adequacy to distinguish between benign and malignant masses, sensitivity and specificity in identifying histotype and grading, also when mixoid area were present.

**Conclusions:** Prof. Mario Campanacci, a great surgeon and teacher, usually said: "Amputation will be done by my youngest assistant, biopsy is my duty". US guided CNB, as part of an interdisciplinary strategy, could be a new way to have good samples for histological diagnosis without any hazard for the correct treatment.

# AN UNBIASED AUTOMATED METHOD OF QUANTIFYING THE FUNCTIONAL CELLULAR HETEROGENEITY OF PROGNOSTIC BIOMARKERS IN TUMOURS

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Claudia Buehneemann<sup>1\*</sup>, Simon Li<sup>2\*</sup>, Haiyue Yu<sup>2</sup>, Harriet Branford White<sup>1</sup>, J Alison Noble<sup>2</sup>, A Bassim Hassan<sup>1</sup> (\*equal contributors)

<sup>1</sup>Sir William Dunn School of Pathology, University of Oxford, UK

<sup>2</sup>Institute of Biomedical Engineering, University of Oxford, UK

**Objectives stating concisely why the study was conducted:** Ewing's sarcoma is the second most common cancer of bone in children and adolescents. It is diagnostically defined by a translocation resulting in the fusion protein EWS/FLI1 which drives the up-regulation of the IGF (Insulin growth factor) pathway. Despite IGF dependency, 70% of patients treated with an IGF1 receptor inhibitor respond poorly. To investigate the basis for this variability in response we have developed unbiased automated segmentation and measurement tools to quantify the heterogeneity in IGF signalling responses.

**Material & Methods:** Tissue microarrays from 119 Ewing sarcoma biopsy samples were labelled with fluorescent antibodies against IGF pathway signalling proteins including pS6, Foxo3a and Egr1, the membrane bound glycoprotein CD99 which is expressed in 95% of Ewing sarcoma, the proliferation marker Ki67, and DAPI. Boundaries for nuclei and cells were identified from the DAPI and CD99 markers using automated and validated algorithms, and measurements of the marker intensities in single cells were obtained and used to create an overall distribution for each patient. Random survival forests (RSF) were used to analyse these marker distributions with respect to patient survival.

**Results:** We found evidence that the distribution of Ki67 is predictive of overall survival as suggested by existing research, and this was confirmed by manual grading of images. Contrary to our expectations the RSF suggested that cells with lower levels of CD99 in the cytoplasm were most discriminative, for reasons which are still to be determined. There was also evidence of differences correlated with the research centres providing the biopsies.

**Conclusions:** We have developed a method for the automated analysis of fluorescently labelled biopsies at a single cell level, and demonstrated its application to predicting patient survival. We have also identified the lack of standardisation in protocols as a confounding factor in the characterisation of tumour heterogeneity.

## HIGH PREVALENCE OF SPECIFIC ANTIBODIES REACTING WITH SV40 CAPSID PROTEIN MIMOTOPES IN SERUM SAMPLES FROM BONE TUMOR PATIENTS.

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Mauro Tognon,<sup>1</sup> Alfredo Corallini,<sup>2</sup> Elisa Mazzoni,<sup>1</sup> Angelo Taronna,<sup>2</sup> Maria Serena Benassi,<sup>3</sup> Piero Picci,<sup>3</sup> Giovanni Carandina,<sup>5</sup> Giovanni Guerra,<sup>5</sup> Ferruccio Casali,<sup>6</sup> Riccardo Dolcetti,<sup>7</sup> Caterina Palmonari,<sup>8</sup> Fernanda Martini,<sup>1</sup> Giovanni Barbanti-Brodano.<sup>4</sup>

<sup>1</sup>Sections of Cell Biology and Molecular Genetics and of <sup>2</sup>Microbiology, University of Ferrara, Ferrara, University of Ferrara, Ferrara. <sup>3</sup>Laboratory of Oncology Research, and <sup>4</sup>Spine Unit, Rizzoli Orthopaedic Institute, Bologna, <sup>5</sup>Clinical Laboratory Analysis, University Hospital St. Anna Ferrara, Ferrara, <sup>6</sup>Clinical Laboratory Analysis, City Hospital of the Repubblica di San Marino. <sup>7</sup>Bioimmunotherapy Unit, Oncology Center, Aviano, <sup>8</sup>Clinical Laboratory Analysis, County Hospital Delta, Ferrara. Italy.

**Objectives:** SV40 is a small DNA tumor virus found to be associated with human bone tumors. SV40 sequences have also been detected, at lower prevalence, in blood specimens from healthy donors. However, some studies have failed to reveal SV40 footprints in human samples, and its association with tumors. The purpose of our study was to verify whether specific antibodies reacting against SV40 are present in human sera from patients affected by bone tumors.

**Materials and Methods:** Our study was addressed to identify in serum samples from bone tumor affected patients and normal individuals antibodies reacting against SV40 VP antigens. Indirect ELISA was set up and developed employing, as antigens, two mimotopes/peptides corresponding to SV40 VP capsid proteins.

**Results:** ELISA data indicate that a high prevalence of SV40 VPs -positive sera was detected in patients affected by osteosarcomas compared to those from normal individuals. No statistically significant difference in prevalence was revealed in sera from patients with breast cancer or undifferentiated nasopharyngeal carcinoma compared to samples from healthy subjects.

**Conclusions:** Our data indicate an association of SV40 with human bone malignancies and that SV40, or a closely related not yet discovered polyomavirus, circulates in the human population.

Andreas Frings<sup>1</sup>, Robert Grimer<sup>2</sup>, Dimosthenis Andreou<sup>3</sup>, Felix Machacek<sup>4</sup>, Karin Pfeiffenberger<sup>1</sup>, Bernadette Liegl-Atzwanger<sup>5</sup>, Per-Ulf Tunn<sup>2</sup>, Andreas Leithner<sup>1</sup>

<sup>1</sup>Department of Orthopedic Surgery, Medical University of Graz, Graz, Austria

<sup>2</sup>The Royal Orthopaedic Hospital Oncology Service, Northfield, Birmingham, UK

<sup>3</sup>Department of Orthopedic Oncology, Sarcoma Center Berlin-Brandenburg, Helios Klinikum Berlin-Buch, Berlin, Germany

<sup>4</sup>Orthopedic Hospital, Gersthof, Vienna, Austria

<sup>5</sup>Institute of Pathology, Medical University of Graz, Graz, Austria

**Objectives:** Tumors of the calcaneus are exceedingly rare. As clinical examination often starts with X-rays, we wanted to ascertain whether X-rays alone were a sufficient diagnostic tool. Diard's classification was applied to define whether different types of lesion were characteristically distributed in the bone. Finally, we wanted to analyze whether type and/or duration of symptoms were possible indicators of malignancy.

**Materials & Methods:** Ninety-two patients' files (59 m, 33 f) were retrospectively reviewed. Parameters analyzed were sex, side, type and duration of symptoms, tentative diagnosis, biopsy prior to surgery, operative procedure, age at surgery, recurrence rate, revision, followup and localization of the lesion according to Diard.

**Results:** Tentative radiological and definitive histological diagnosis differed from each other in 38 (41%) of 92 cases. In eight (osteosarcoma n = 5, Ewing's sarcoma n = 2, metastases n = 1) of 17 malignant cases radiological examination initially gave no evidence of malignancy, resulting in an unplanned excision ("whoops procedure") in three cases of osteosarcoma. Applying Diard's system trabecular area number 6 (radiolucent area) was highly affected in 64 (80%) of 80 investigated plain X-rays.

**Conclusions:** In each case of an osteolytic lesion of the calcaneus a malignant tumor must be ruled out and thus, preoperative plain X-rays in two planes alone are not sufficient and should therefore be followed by MRI. Applying the Diard system different types of lesions are not characteristically distributed in the bone. Increasing pain without medical history for more than ten days should always justify further examinations.

## NEUROTHEKEOMA- A RARE BENIGN NERVE SHEATH TUMOR: A CASE REPORT

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M. Ornig, J. Friesenbichler, W.Maurer- Ertl, B. Liegl-Atzwanger, A. Leithner

Department of Orthopedic Surgery, Medical University of Graz, Austria.  
Institute of Pathology, Medical University of Graz, Austria.

**Introduction:** Neurothekeoma is an extremely rare benign soft tissue tumor of nerve sheath origin with fairly distinctive histological features characterized in a variable myxomatous stroma. These tumors can mainly be found in head , neck and upper extremities. The 'classic' type has been reported in middle aged adults, the 'cellular' type has been observed in younger adults, more common in females. The treatment of choice is resection with clear margins.

**Case:** Here we present the case of a 25- year old woman with a neurothekeoma of the suprapatellar region, accidentally found during the removal of osteosynthetic material in proximal tibial area. After non in sano resection of the tumor, the patient was admitted to our department for a wide surgical excision. In the surgical specimen tumor foci were still present. The patient was discharged after a few days, MRI controls were scheduled.

**Conclusion:** Reporting such a case should increase awareness about the possible differential diagnosis of neurothekeoma. The treatment of choice is a resection with marginal or wide surgical margins.

*Jun Takada, Manabu Hoshi, Naoto Oebisu, Masanari Aono, Makoto Ieguchi, Masatsugu Takami, Hiroaki Nakamura*

*Department of Orthopedic Surgery, Graduate School of Medicine, Osaka City University – Osaka - JAPAN*

**Objectives:** Simple bone cysts are benign cystic lesions, mainly seen in childhood. Pathological fracture may be repeated, and various treatment methods have been reported. To this moment, little can be definitely said on etiology or on rationale for treatment. The aim of the present study was to analyze the cyst fluid and evaluate the clinical characteristics of simple bone cysts, to seek a key to pathogenesis and efficient treatment.

**Material and Methods:** Cyst fluid was obtained during the operation, from 31 cysts in 31 patients which were surgically treated. There were 22 male and 9 female patients, and mean age at surgery was 11.8 years (5 to 18). The cyst was located in the calcaneus in 14 patients, in the humerus in 12, and in the femur in 5. Curettage and grafting with bone substitute material was performed in 25 patients, and 6 patients were treated with cannulated pins. Cyst fluid was compared with blood serum obtained preoperatively.

**Results:** Secondary procedure was performed due to recurrence in 5 cysts. No recurrence was seen in the calcaneal cysts. In the biochemical studies of cyst fluid, alkaline phosphatase (ALP) concentration was significantly higher than that in the blood serum. ALP concentration of cyst fluid in calcaneal cysts was significantly lower than that in other sites, whereas cholesterol concentration was significantly higher.

**Conclusions:** The cyst fluid is similar to blood serum, but shows signs of increased bone turnover. In calcaneal cysts, the good prognosis, the low ALP concentration and high cholesterol concentration in cyst fluid, suggests difference in etiology.



# A NOVEL SPECIFIC GENETIC TRANSLOCATION IN EPITHELIOID HEMANGIOENDOTHELIOMA SHOWING A FUSION OF THE WWTR1 AND CAMTA1 GENES.

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<sup>1</sup>Costantino Errani; <sup>2</sup>Cristina R. Antonescu; <sup>1</sup>Cesare Faldini; <sup>2</sup>John H. Healey.

<sup>1</sup>Rizzoli-Sicilia, Bagheria, Italy; <sup>2</sup>Memorial Sloan Kettering Cancer Center, New York, NY.

**Objectives:** The terminology and the classification of vascular tumors remain considerable controversy. We hypothesize that a better understanding of the molecular signature of vascular tumors may help to refine the present classification system based on immunophenotype alone. A prior t(1;3)(p36.3;q25) was identified in 2 cases of epithelioid hemangioendothelioma (EHE), however no follow-up studies have been performed to identify the gene fusion or to assess its prevalence in a larger cohort of patients.

**Material and Methods:** In this study, we performed a systematic molecular analysis of 17 cases of EHE, characterized by classic morphologic and immunophenotypic features, including lesions arising from various anatomic locations and lesions with different biological potentials. Gene rearrangements were analyzed by fluorescence in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (RT-PCR). Also included for comparison was a group of epithelioid hemangioma, epithelioid angiosarcoma and epithelioid sarcoma..

**Results:** An identical genetic translocation involving the CAMTA1 and WWTR1 genes, respectively on chromosomes 1 and 3 [t(1;3)(p36.23;q25.1)] was shown by FISH in all cases. RT-PCR applied in 3 tumors with available frozen tissue confirmed the chromosomal rearrangement. None of the other vascular tumors examined had a WWTR1-CAMTA1 fusion.

**Conclusion:** CAMTA1 and WWTR1 genes have been shown to play an important role in oncogenesis. Our results demonstrate the presence of *CAMTA1-WWTR1* fusion in all EHE tested from bone, soft tissue and visceral location (liver, lung) in keeping with a single tumor entity. This chromosomal translocation may serve as the ultimate biomarker for EHE, as it appears to be specific for this distinct histopathologic tumor type, so it may help to differentiate EHE from other vascular tumors. Furthermore, as more oncogenic properties of the WWTR1-CAMTA1 fusion protein and cooperative events are elucidated, therapeutic strategies can be tailored to interrupt these oncogenic processes.

Vânia Oliveira, Luís Costa, Daniel Freitas, Ricardo Aido, Ricardo Sousa, Eurico Silva, José Figueiredo, Pedro Cardoso

Oporto Hospital Center – Santo António Hospital Oporto – Portugal Orthopaedics and Traumatology Department [vaniacoliveira@gmail.com](mailto:vaniacoliveira@gmail.com)

**Introduction and Objective:** Lumbosacral lipoma is a particular group that is extremely rare and deserves recognition because of its close relation to the spinal cord and its coverings. It is characterized by a diffuse proliferation of mature fat and can be intradural or extradural. They are always associated with spina bifida or a similar laminar defect or sacral dysgenesis. Clinically, it tends to be initially asymptomatic and when the diagnosis is made a large infiltrative tumor is expected.

CT and MR images are essential for diagnosis and for therapy planning. However, because of large size, deep location and infiltrating growth pattern, the distinction between lipoma and well-differentiated liposarcoma is difficult and biopsy is mandatory.

Total resection with laminectomy and division of the stalk and fibrous bands that have formed at the upper margin of the spinal defect has a good prognosis and should be performed as early as possible, preferably prior to the onset of neurologic symptoms. However, does not always prevent the development of leg paralysis and neurogenic bladder. In case of subtotal excision, the recurrence rates reported in the literature vary widely.

As opposed to superficial lipomas, little is known about the etiology or histogenesis of intramuscular lipomas. This case report is a rare lumbosacral lipoma to increase knowledge about this particular entity of lipomas.

**Case Report:** A thirty-five year old female presented low back pain radiating to the right buttocks, without neurological changes, with an evolution of 2 years and progressive worsening. It was associated to a large right paraspinal tumor, painless on palpation, softened consistency and deep-seated. The patient has no congenital disorders or anatomical defects.

Imaging study revealed a large bilateral intramuscular infiltrative mass lesion from L2 to S1, homogeneous, extradural, with paraspinal muscular atrophy and fatty degeneration, right predominance, without any neurological compromise. The differential diagnosis was intramuscular lipoma with well-differentiated liposarcoma.

The result of the incisional biopsy was compatible with a lipoma. The surgical resection was intralesional because of the infiltrative margin and close relation to neurological structures. The histopathological examination confirmed the diagnosis of intramuscular infiltrative lipoma, without malignant changes. The patient has no recurrence at 1-year follow-up.

**Discussion:** Lumbosacral lipoma is a rare entity and is always associated with spina bifida or a similar laminar defect, and there is a stalk-like connection between the fatty growth and a portion of the spinal cord that often also harbors an intradural or extradural lipoma. The stalk may cause traction and ischemia.

This lumbosacral lipoma is a particular case that presents posterior extradural lipomatosis at L3-L4 associated with thickening of the ligamentum flavum and deformity of the posterior epidural fat, although it does not present any congenital anomalies.

Vânia Oliveira<sup>1</sup>, Luís Costa<sup>1</sup>, Daniel Soares<sup>1</sup>, Daniel Freitas<sup>1</sup>, Luciana Leite<sup>1</sup>, Ricardo Aido<sup>1</sup>, Rui Machado<sup>2</sup>, Pedro Cardoso<sup>3</sup>

<sup>1</sup> Resident of Orthopaedics

<sup>2</sup> Hospital Assistant of Vascular Surgery

<sup>3</sup> Hospital Assistant of Orthopaedics

Orthopaedics and Traumatology Department – Musculoskeletal Tumors Group OPorto Hospital Center – Santo António Hospital Oporto – Portugal [vaniacoliveira@gmail.com](mailto:vaniacoliveira@gmail.com)

**Introduction and Objective:** Primary venous leiomyosarcomas arise from vascular smooth-muscle cells and growth pattern may progress from intramural to endoluminal, extraluminal or mixed forms. In the literature, leiomyosarcoma of vascular origin is rare and most commonly affects the larger veins such as the inferior vena cava.

Symptoms are defined by the anatomic location of the lesion, local vascular physiology and drainage patterns. The definitive diagnosis is often delayed and complete resection is usually not possible. Metastatic disease occurs in a half of patients at the time of diagnosis. However, an aggressive surgical approach assuring a free margin tumour resection can be curative despite reported local recurrence rates in selected cases of 40 to 60%. It has a poor prognosis and multidisciplinary teamwork is essential.

The aim of this case report is to remember this pathology that comprises a seemingly rare group of tumors illustrated by the fact that only a few hundred cases have been reported in the literature.

**Case Report:** An eighty-three years old female presented a 4 months evolution tumor at the right popliteal fossa, 4x6cm, hardened consistency and adherent to deep planes. She had numbness and oedema of the lower leg and a dorsal pedal pulse was present.

MRI revealed a tumor involving the entire tibial neurovascular bundle. The diagnosis of pleomorphic leiomyosarcoma of high degree of malignancy was achieved by Tru-Cut needle biopsy.

Staging imaging studies did not revealed distant metastasis. The lower limb arteriogram showed intact arterial flow of anterior and posterior tibial artery.

Wide tumor excision was performed. The sacrifice of the tibial nerve and anterior tibial artery was necessary and the left great saphenous vein was inverted and anastomosed end-to-end to the tibioperoneal arterial trunk.

The diagnosis of primary venous leiomyosarcoma and free margin resection were confirmed by histopathology.

The patient presents a favourable functional outcome and is disease free after one year of follow-up.

**Discussion:** The morbidity and mortality associated with these tumors are primarily a result of direct extension of the tumor along vessels, compromising the circulation.

One of the greatest problems when treating this disease is that the localization itself may preclude surgical resection but in this case the localization permitted a safe free-margin excision.

Nuno Vieira Ferreira<sup>1</sup>, Rui Duarte<sup>1</sup>, Luís Miguel Silva<sup>1</sup>, Luís Filipe Rodrigues<sup>1</sup>, Ricardo Maia<sup>1</sup>,  
Nuno Sevivas<sup>2</sup>, César Silva<sup>3</sup>, M. Vieira da Silva<sup>4</sup>

\*At Hospital de Braga, Portugal

1. Orthopedic Surgery department, Resident, Braga Hospital, Braga, Portugal
2. Orthopedic Surgery department, Chairman Shoulder Unit, Braga Hospital, Braga, Portugal
3. Orthopedic Surgery department, Chairman Hand Unit, Sto António Hospital, Porto, Portugal
4. Chairman Orthopedic Surgery Department, Braga Hospital, Braga, Portugal

**Purpose:** Schwannomas are the most common neurogenic tumours of the torax, especially in the posterior mediastinum, whereas in the peripheral nervous system they are relatively uncommon. Only about 5% arise from the brachial plexus but should always be considered in the differential diagnosis of shoulder pain. Due to its rarity and complex anatomical location they can be a challenge to orthopaedic surgeons.

We present a case of a 57-year-old man referred to our centre after six months of shoulder pain, with no other complaints.

**Methods:** Complete shoulder pain investigation was done and MRI suggested a 4,5x3,5cm brachial plexus tumour. Schwannoma was diagnosed by ultrasound-guided biopsy.

Surgical exploration showed the tumor arising from the fascicles of brachial plexus and complete tumor excision was done.

**Results:** The patient had no sign of neurological disorders postoperatively and 8 weeks after surgery returned to his active life with no pain or limitation.

**Conclusion:** Complete surgical excision is the most indicated treatment for schwannoma. Even in rare anatomical locations, it is very effective.

Beware of neurogenic tumours when considering shoulder pain differential diagnosis.

Nuno Vieira Ferreira<sup>1</sup>, Rui Duarte<sup>1</sup>, Ricardo Maia<sup>1</sup>, Luís Miguel Silva<sup>1</sup>, Nuno Sevivas<sup>2</sup>, Ramiro Fidalgo<sup>3</sup>, M. Vieira da Silva<sup>4</sup>

*\*At Hospital de Braga, Portugal*

1. Orthopedic Surgery department, Resident, Braga Hospital, Braga, Portugal
2. Orthopedic Surgery department, Surgeon, Braga Hospital, Braga, Portugal
3. Orthopedic Surgery department, Chairman Knee Unit, Braga Hospital, Braga, Portugal
4. Chairman Orthopedic Surgery department, Braga Hospital, Braga, Portugal

**Purpose:** “Ganglion” is a rare cystic lesion, usually asymptomatic without any classic signs. Rarely described in the knee, when they appear, these lesions are usually of small dimension. There are very few cases of giant “ganglion” reported.

The authors present the case of a 47-year old male patient who had an infra-patellar mass in the left knee, with 5 years of progressive growth, spherical, with about 10cm in diameter.

**Methods:** Surgical tumor excision was done by cross-cutting approach with skin flap following the cleavage plane.

**Results:** Follow-up performed 4 weeks after surgery revealed that the patient was asymptomatic and returned to his active life.

**Conclusion:** The case presented is uncommon either by location or by the size of the lesion.

Magnetic Resonance Imaging (MRI) characterized the lesion and its relations with neighboring structures. Giant “ganglion” is an extremely rare benign knee injury and surgical excision demonstrated to be an effective treatment.

Alessandro Franchi,<sup>1</sup> Annarita Palomba,<sup>1</sup> Giuliana Roselli,<sup>2</sup> Claudio Gambini,<sup>4</sup>  
Giovanni Beltrami,<sup>3</sup> Rodolfo Capanna,<sup>3</sup> Domenico Campanacci<sup>3</sup>

Units of Histopathology,<sup>1</sup> Radiology,<sup>2</sup> and Orthopedic Oncology,<sup>3</sup> Azienda Ospedaliera Universitaria, Careggi, Florence, Italy  
Unit of Pathology,<sup>4</sup> Department of Clinical Diagnostics and Radiology, IRCCS Giannina Gaslini, Genoa, Italy

**Objectives:** Myoepithelial tumors (MT) are increasingly recognized at extra-salivary anatomic sites, including the bone and soft tissues. Overall, in the extragnatic skeleton they are exceedingly rare neoplasms, and their clinico-pathological features have been described only in single case reports. The objective of this presentation is to describe the clinico-pathological, immunohistochemical and molecular features of three primary juxtacortical MT of bone.

**Materials and Methods:** Clinical charts, imaging studies and paraffin embedded tumor tissue fragments were retrieved from our files.

**Results:** The patients were two male subjects (13 and 23 years of age) and a 15-year-old female. The juxtacortical lesions were all located in the femur, and involved the adjacent soft tissues and cortical bone. All patients underwent surgical resection of the tumor, two with wide margins and one with marginal margins. This latter tumor recurred locally 18 months later, and it was removed with wide margins. The three patients are currently free of disease at 4 to 17 months follow-up. Histologically, all lesions showed a prominent multinodular architecture, and were formed by epithelioid and stellate elements, with little or no atypia, organized in solid sheets or embedded in myxoid or chondroid matrix. Areas of osteoid formation were also observed. One tumor had the appearance of classical mixed tumor, showing aspects of duct formation and focal squamous differentiation. Immunohistochemically, all cases showed diffuse and intense positivity for cytokeratins, EMA and S100 protein. The expression of other myoepithelial markers, including GFAP and calponin was more limited. The notochordal marker brachyury was negative, while diffuse nuclear immunostaining for INI-1 was observed in all lesions. The three tumors were screened for the presence of EWSR1 and FUS gene abnormalities by fluorescent in situ hybridization, and no rearrangement was observed.

**Conclusions:** To our knowledge, this is the first report of primary MTs of bone arising at juxtacortical sites. These lesions must be distinguished from other benign and malignant bone and cartilage forming surface tumors, including periosteal chondroma and chondrosarcoma, juxtacortical chondromyxoid fibroma, and periosteal and paraosteal osteosarcoma. The clinico-radiologic presentation and their histological and immunohistochemical features are distinctive enough to allow the separation from these entities. Overall, juxtacortical MTs appear to behave as locally aggressive tumors, that should be surgically removed with wide margins.

## DIFFUSE PIGMENTED VILLONODULAR SYNOVITIS OF THE FOOT AND ANKLE: OUTCOMES AFTER AGGRESSIVE COMPLETE SYNOVECTOMY

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JD Stevenson, A Jaiswal, JJ Gregory, G Cribb, P Cool

Greater Manchester and Oswestry Bone and Soft Tissue Tumour Service, Robert Jones & Agnes Hunt Orthopaedic Hospital, UK

**Introduction:** Pigmented villonodular synovitis (PVNS) is a rare benign aggressive disease of the synovium of weight-bearing joints and tendon sheaths. There are two forms of the disease: diffuse and localised (nodular). It affects the foot and ankle in less than 10% of cases. Patients complain of localised swelling and/or pain. Typically monoarticular, it can be locally erosive, and synovectomy is the well described management. Treatment outcomes are poorly understood; we aimed to review our results using aggressive complete synovectomy.

**Materials and Methods:** We followed up 24 patients with histologically confirmed PVNS in a prospective study between 2000 and 2011; 7 were excluded with localised (nodular) PVNS. After local ethical approval, questionnaires including the Toronto Extremity Survival Score (TESS) were posted to patients, and non-responders were reminded to return their forms by telephone. The response rate after reminder was 100%.

**Results:** Seventeen patients have been prospectively followed for mean 4.8 years (range 1-11.3 years). Six patients were male, 11 female. Mean age at presentation was 42 years (range 10-73 years). All histological samples were classified as diffuse PVNS and involved articular joints of the foot and ankle. All patients had Magnetic Resonance Imaging at presentation. Thirteen of the 17 patients underwent aggressive complete synovectomy, all without radiotherapy. The four non-operatively managed patients remain asymptomatic and under clinical and radiological surveillance. Mean Toronto Extremity Survival Score was 91.55 (95% CI 3.3 to 6.5) at final follow-up. There was one case of radiological recurrence in the surgical group which resolved radiologically without further intervention. No patients have required arthrodesis to date.

**Conclusions:** This demonstrates satisfactory medium-term outcomes in this rare disease with surgical debridement alone.



# OSTEOSARCOMA ARISING FROM OSTEOCHONDROMA OF THE TIBIA: CASE REPORT AND CYTOGENETIC FINDINGS

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*Edgard E. Engel, Marcello H. Nogueira-Barbosa, Maria Sol Brassesco, Gyl E.B. Silva, Elvis T. Valera, Fernanda M. Peria, Tatiane C. Motta and Luis G. Tone*

*Faculty of Medicine of Ribeirão Preto / University of São Paulo*

Osteochondroma is a cartilage capped benign tumor developing mainly at the juxta-epiphyseal region of long bones. The rate of malignant transformation, mainly into chondrosarcoma, is estimated to be less than 1-3%. Transformation into osteosarcoma is very rare and has been reported only thirteen times. There is little information on treatment and outcome. We report the case of a secondary osteosarcoma arising in the left tibia of a 23-year-old male, 10 years after the initial diagnosis of osteochondroma and after two partial resections. Malignant transformation occurred at the stalk and not at the cartilage cap, as would normally be expected. Chromosome banding analysis revealed the karyotype: 46,XY, t(3;13)(q21;q34) [2]/46,XY [18]. Records from additional cases will help determine the parameters that define these rare secondary bone lesions.

# DESMOPLASTIC FIBROMA OF BONE: A TERTIARY TUMOUR UNIT'S EXPERIENCE.

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Mr S. Evans<sup>1</sup> MBChB MRCS. St4 Trauma and Orthopaedics

Mr L. Jeys FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon

Mr A. Abudu FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon

Mr R. Tillman FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon

Mr S. Carter FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon

Mr R. Grimer FRCS (Tr+Orth)<sup>1</sup>. Consultant Orthopaedic Surgeon

<sup>1</sup> Royal Orthopaedic Hospital, Birmingham, Birmingham, UK.

Lead author: Mr. Scott Evans. Email: drscottbevans@yahoo.co.uk

Royal Orthopaedic Hospital, Birmingham

**Aim:** Identify treatment modalities and local recurrence rates.

**Methods:** Retrospective review of a prospectively collected database amassed over 25 years. Patient demographics were recorded along with management and local recurrence rates.

**Results:** 11 patients identified. 4 male, 7 female. Mean age at presentation 29.7 years. All referred to our unit with pain and/or swelling to the affected area; 8 lower limb, 3 upper limb. 5 patients treated with detailed curettage. Of those patients, 1 developed significant local recurrence and required a below knee amputation to control the disease. 2 patients underwent attempted wide-local excision. Both had positive margins on histological analysis but neither developed local recurrence at two-year follow-up. 1 patient underwent primary endo-prosthetic replacement of the proximal tibia. Wide excision margins were found on histological review and, at 13 years post primary replacement, no local recurrence has been identified. 2 patients refused any surgical intervention. 1 patient was lost to follow-up.

**Conclusion:** Desmoplastic fibroma is an extremely rare tumor. The 1 patient in our series who required a below knee amputation due to local recurrence had presented with pain and swelling to right ankle. Radiological examination revealed near complete destruction of the calcaneum, with biopsy confirming desmoplastic fibrosis. Detailed curettage was attempted but the patient had no relief from pain. A below knee amputation was, therefore, performed. From our review, excision seems to provide adequate disease control even with positive histological margin and we would advocate wide-local excision as primary surgical management.

*Bahtiyar Demiralp, Department of Orthopaedics and Traumatology, Gülhane Military Engin İlker Cicek, Department of Orthopaedics and Traumatology, Golcuk Military Hospital, Kocaeli/Turkey  
Bulent Kurt; Pathology, Gülhane Military Medical Academy, Ankara, Turkey  
Mert Keskinbora; Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey  
Cagri Neyisci; Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey  
Mustafa Basbozkurt Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey*

**INTRODUCTION:** Intraosseous hemangioma is a rare bone tumor, accounting for less than 1% of bone neoplasms. In most cases, the tumor that is progressing slowly is located in the skull or vertebrae. When the disease arises in long bones, most cases are located in the metadiaphysis or diaphysis. Epiphyseal-based juxta-articular hemangiomas of long bones have rarely been reported.

**OBJECTIVES:** Although the first preliminary diagnosis that comes to mind in patients of young adult age group with epiphyseal localized tumors are chondroblastoma, giant cell tumor of bone, chondromyxoid fibroma, this study aims to emphasize that exceptional results can occur. as like our case.

**METHODS:** Fifty-year-old-male had progressive left knee pain for 4 years. His medical history, the physical examination and routine laboratory tests were normal. Left knee AP / L showed an osteolytic lesion in proximal left tibia epiphysis. This lesion was approximately 2x2 cm with no cortical involvement. Limited marginal sclerosis was identified. Chondroblastoma and giant cell tumor of bone were preoperatively considered as preoperative diagnosis.

**RESULTS:** Histopathologic diagnosis was intraosseous hemangioma as a result of excisional biopsy.

**CONCLUSIONS:** As a rare tumoral lesion, intraosseous hemangioma could also be considered in the differential diagnosis of epiphyseal located bone tumors.

## OSTEOID OSTEOMA: THE DELAYING AND CHALLENGING DIAGNOSED CASES

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*Engin Ilker Cicek, Department of Orthopaedics and Traumatology, Golcuk Military Hospital, Kocaeli/Turkey*

*Bahtiyar Demiralp, Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey*

*Selim Sanel, Department of Orthopaedics and Traumatology, Golcuk Military Hospital, Kocaeli/Turkey*

*Mert Keskinbora; Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey*

*Mustafa Basbozkurt Department of Orthopaedics and Traumatology, Gülhane Military Medical Academy, Ankara, Turkey*

**Objectives:** The aim of this study is to illustrate the difficulties in the diagnosis of osteoid osteoma and the role of imaging modalities and medical evaluations in the patients with chronic pain and sometimes limited ROM treated with unrelated diagnosis. Also, we aim to point out the diagnostic clues and follow up modalities related actual literature reviews.

**Material and Method:** We retrospectively search our cases diagnosed as osteoid osteoma. Their history and diagnostic studies were evaluated. We add the challenging and delayed cases for diagnosis of osteoid osteoma in our study.

**Results:** Osteoid osteoma is a relatively common benign skeletal neoplasm of unknown etiology that is composed of osteoid and woven bone. This lesion can occur in any bone, but in approximately two thirds of patients there is a predilection for the appendicular skeleton, with %50 or more of lesions occurring in the femur and tibia. The characteristic radiolucent nidus, that is believed to be responsible for severe pain, may not always be present. Although, the clinical, radiological and scintigraphic features of osteoid osteoma have been well described, they can be misleading or altered, especially in the cases of intraarticularly or metaphyseally located tumors.

**Conclusion:** When the lesion is localized intra-articularly or metaphyseal, the other diagnosis related to that joint can be delayed the real diagnosis and cause osteoid osteoma to be overlooked.

*Engin Ilker Cicek, Golcuk Military Hospital, Orthopaedics and Traumatology Department, Kocaeli/Turkey.*

*Bahtiyar Demiralp, Gulhane Military Medicine Academy, Orthopaedics and Traumatology Department, Ankara/Turkey*

*Mustafa Başbozkurt, Gulhane Military Medicine Academy, Orthopaedics and Traumatology Department, Ankara/Turkey*

*Selahattin Ozyurek, Izmir Military Medicine Academy, Orthopaedics and Traumatology Department, Izmir /Turkey*

*Selim Sanel, Golcuk Military Hospital, Orthopaedics and Traumatology Department, Kocaeli/Turkey.*

Chondromyxoid fibroma is rarely seen benign bone tumor of cartilage origin observed less than 0.5 to 1% of all skeletal neoplasms and was first described by Jaffe and Lichtenstein as a distinctive benign tumor.

Chondromyxoid fibroma occurs in almost any osseous site. It is most frequent in the long bones including proximal tibia and distal femur. Chondromyxoid fibroma in a long bone is typically in a metaphyseal as an eccentric, sharply marginated tumor. Rarely, bones are affected contiguously or the tumor may be juxtacortical. Chondromyxoid fibroma is commonly presented in the second and third decades of life. However, it was rarely reported in the first decade.

We presented a 6-year-old child with pain and gradually enlarging mass on the superolateral aspect of the right knee for 5 months. Evaluation of the histopathologic and radiologic images was confirmed our diagnosis of chondromyxoid fibroma of bone

We discussed this case as its rarity and importance in distinctive diagnostic evaluation.

Levin D<sup>1</sup>, Kollender Y<sup>2</sup>, Issacov J<sup>3</sup>, Elhasid R<sup>1</sup>

Tel-Aviv Sourasky Medical Center Israel 1-Pediatric Hemato-Oncology department ,2- Oncological Orthopedic Oncology department, 3- Pathology department.

Neurofibromatosis type 1( NF1) is un autosomal dominant disorder that affects one in 3000 live births. NF1 predisposed for both benign and malignant tumors. The typical benign tumors are Neurofibroma and Schwannoma, while the typical malignant tumors are Malignant peripheral nerve sheath tumor and Rhabdomyosarcoma.

We present three cases of NF1 patients who had unexpected diagnosis of bone or soft tissue tumor. One patient had benign rare tumor (Brown tumor) and two patients had relatively rare malignant tumor (triton tumor and synovial sarcoma).

We review the literature on soft tissue tumors in NF1 patients and emphasize the broad spectrum differential diagnosis.

Bartoli MS<sup>1</sup>, Gaston CL<sup>2</sup>, Sumathi V<sup>2</sup>, Abudu S<sup>2</sup>, Carter SR<sup>2</sup>, Jeys LM<sup>2</sup>, Tillman RM<sup>2</sup>, Grimer RJ<sup>2</sup>

<sup>1</sup>*Scuola di Specializzazione in Ortopedia e Traumatologia, Università degli Studi di Milano, Italy* <sup>2</sup>*Royal Orthopaedic Hospital Birmingham, UK*

**Introduction:** Atypical lipomatous tumours (ALT) are common large soft tissue tumours arising in limbs. Treatment is marginal excision to prevent them from increasing in size and avoid the risk of dedifferentiation. This study investigates risk factors for dedifferentiation of ALT.

**Methods:** All patients with a diagnosis of either ALT or dedifferentiated liposarcoma arising in the limbs or limb girdle were included and risk factors for dedifferentiation were investigated.

**Results:** There were 290 patients with ALT who never had any dedifferentiation and in whom local recurrence occurred in 11% at a mean time of 51.5 months from the first excision (range 4 – 162 months). The mean time for dedifferentiation was 12 years from original diagnosis (range 2 – 34 years) with patients having 2 – 4 local recurrences prior to dedifferentiation. Dedifferentiation was significantly associated with ALT with local recurrence and >2 excisions on univariate and multivariate analysis. The risk for dedifferentiation was 2% at 5 years and 6% at 10 years in patients who had undergone excision of an ALT. This risk increased to 9% and 22% respectively in patients who had a local recurrence. Metastases occurred in 43% who had dedifferentiation while none were seen in patients with ALT.

**Conclusions:** Marginal excision remains the treatment of choice for atypical lipomatous tumours. Dedifferentiation is a rare complication of ALT and must be suspected in patients who have multiple local recurrences after excision. Regular follow-up may be recommended for those who have had more than 2 local recurrences.



## DERMATOFIBROSARCOMA OF THE ANKLE IN A 2 YEAR OLD BOY

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U.M. Pirker-Frühauf, J. Friesenbichler, W. Maurer-Ertl, A. Leithner

Dept. of Orthopaedic Surgery, Medical University Graz, Graz, Austria

**INTRODUCTION:** Dermatofibrosarcoma protuberans (DFSP) presents the most common sarcomatous tumour of the skin. Nevertheless, its occurrence is very rare, usually affecting young adults. The tumour grows locally aggressive with high recurrence rates after resection. Slowly growing, DFSP is mainly localized on the trunk or trunk-close parts of the extremities. In most cases it presents immunohistochemical characteristics and a translocation between chromosomes 17 and 22, which helpfully supports diagnosis. First line therapy is a wide local excision. Further, therapeutic success has been reported with Imatinib in advanced disease.

**CASE PRESENTATION:** We report the case of a 2-year old boy with histological verified dermatofibrosarcoma protuberans of the left lateral ankle. The patient was assigned to our department after non-in-sano resection of the lesion, which primarily presented itself as a therapy resistant swelling for about two months. A lipoma (2.8x0.7x2.9cm) was first line diagnosed by ultrasound. Histology of the intralesional resection tissue presented the micromorphology and immunohistochemistry of partly a giant cell fibroblastoma (a juvenile form of the dermatofibrosarcoma protuberans) as well as parts of DFSP. Follow-up-MRI showed a local recurrence after one year. The following wide resection was performed at our department. Primary staging was done by computer tomography (lungs) and ultrasound (lymph nodes/abdomen). Follow up will include local MRI and abdominal ultrasound, no systemic therapy.

**CONCLUSION:** We focus on a very rare entity of tumour, which occurred atypically concerning age and localization. Our main intent is to sensitize that dermatofibrosarcoma protuberans should be considered as a potential diagnosis in young sarcoma patients.

*J. Panotopoulos, PT. Funovics, V. Stockhammer, J. Holinka, R. Windhager, A. Wanivenhaus*

*Department of Orthopaedics, Medical University of Vienna, Austria*

**Objectives:** Hemophilic pseudotumor was defined by Fernandez de Valderrama and Matthews as a progressive cystic swelling involving muscle, produced by recurrent hemorrhage and accompanied by roentgenographic evidence of bone involvement. The most common site for the hemophilic pseudotumor is the proximal skeleton around the femur and pelvis.

**Methods:** We retrospectively reviewed all clinical histories of 87 patients with bleeding disorders treated between 1967 to 2011 because of musculoskeletal affection due to congenital bleeding disorders. We identified 6 patients with a hemophilic pseudotumor who were treated at our department.

**Results:** The mean age at surgery was 45.9 (range: 40-61) years. The iliac bone was affected in 3 patients (one right, two left), the right tibia (distal diaphysis) in one, the right thigh in two and the right ulna (proximal part) in one patient. One patient had two pseudotumors. The perioperative course was easily controllable with adequate factor VIII substitution. At the latest follow up after 8.4 (4-24) years, normal healing with no recurrence was observed.

**Discussion:** The hemophilic pseudotumor is a rare but severe complication of hereditary bleeding disorders. In the international literature the resection and postoperative course are described as challenging and difficult and as requiring detailed preoperative planning. Operation done in specialised centres with close cooperation between surgeons and hematologists is advisable.

**Keywords:** Hemophilic pseudotumor, Haemophilia, Surgery

# TUMOR-TO-TUMOR METASTASIS: MALE BREAST CARCINOMA METASTASIS ARISING IN AN EXTRAPLEURAL SOLITARY FIBROUS TUMOR – A CASE REPORT.

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S. Scheipl<sup>1</sup>, E.V. Froehlich<sup>1</sup>, B. Rinner<sup>2</sup>, B. Lohberger<sup>1</sup>, F. Moinfar<sup>3</sup>, A. Leithner<sup>1</sup>, B. Liegl<sup>3</sup>.

<sup>1</sup> Department of Orthopaedics and Orthopaedic Surgery, Medical University Graz, Austria

<sup>2</sup> Center for Medical Research, Cell Culture Facility, Medical University of Graz, Austria

<sup>3</sup> Institute of Pathology, Medical University of Graz, Austria

**Background:** Tumor-to-tumor metastases are rare, but well-documented findings. This term refers to one tumor metastasizing to another tumor within the same individual. We report a unique case of a male breast cancer metastasis occurring in a solitary fibrous tumor (SFT) which was located in the subcutaneous tissue of the back of a 68 year-old patient. SFTs are rare, intermediate grade and seldom metastasizing mesenchymal neoplasms commonly occurring in subcutaneous tissue.

**Case Report:** A 68 year-old male suffered from a painless nipple inversion of the right breast for nearly one year. He was diagnosed with breast cancer in March 2006 (mixed-typed ductal-lobular). In addition to mastectomy and axillar dissection, he was treated with local irradiation therapy and (neo-) adjuvant chemotherapy. Nevertheless, metastases to the lung and the bone were diagnosed 45 months after initial diagnosis. In course of further staging, attention was drawn to a subcutaneous expansion located at the left side of his back (level Th2-3). The patient had noticed this painless expansion for about fifteen years, with a minor progression during the last 12 months. To exclude a soft-tissue breast cancer metastasis, excision biopsy was performed. Macroscopic examination revealed a solid, grayish lesion with a maximum diameter of 8 cm. Histological examination showed a mesenchymal tumor composed of bland round to spindle shaped tumor cells with indistinct cell borders. The tumor cells were set in and collagenous stroma, and arranged in a "pattern less" pattern. Mast cells were also present. A prominent haemangiopericytoma-like vascular pattern was seen. Mitosis were scarce (2/10 HPF). Within the tumor, nests of epithelial cells and ductal structures were seen.

**Immunohistochemistry:** The mesenchymal spindle cell component showed a strong positivity for antibodies (AB) against CD34 and was completely negative for various CKs and EMA. However, the ductal epithelioid structures showed a strong positivity for AB against various CKs, EMA, Estrogen and Progesterone, but were negative for PSA. In addition, a, HER-2/neu overexpression was detected. The diagnosis of a SFT hosting a metastasis of a male breast cancer was made. The patient received palliative chemotherapy and is alive with disease 71 months after initial diagnosis.

**Discussion:** The spreading of carcinomas to mesenchymal tumors has been described in the context of tumor-to-tumor metastases. Among mesenchymal neoplasms, particularly benign and low-grade malignant lesions seem to be involved. Pleural SFT has once been reported as host for a renal cell carcinoma metastasis. Possibly, the high vascularisation of SFTs may contribute to their role as hosts for haematogeneous metastases. Although breast cancer is a well-documented donor to tumor-to-tumor metastasis, male breast cancer is a rare entity by itself, and particularly in this setting. In summary, this case combines several uncommon findings which have – to the best of our knowledge – not been described before.

Luciana Leite, Daniel Soares ; Pedro Leite; Luis Costa ; Vânia Oliveira; Pedro Cardoso

Orthopedic Surgical Department - Hospital de Santo António – Oporto - Portugal

**Objectives:** Aneurysmal bone cyst is a benign, locally destructive lesion of bone. According to WHO, this affection is an expansive osteolytic lesion consisting of spaces filled with blood in any segment of the skeleton, being most frequently encountered in the diaphysis of the long bones or spinal cord and can arise in many benign tumours and pseudotumours.

This paper reports a case of aneurysmatic bone cyst with an aggressive behavior, arising in a desmoplastic fibroma, imposing a wide resection.

**Material and Methods:** Case report of a female patient, 11 years, with an aneurysmal bone cyst of proximal humerus diagnosed accidentally in 2006 after a fall from which resulted an osteolytic fracture. This lesion was interpreted as a simple bone cyst, and the fracture was treated conservatively, with good clinical evaluation. Patient's lesion remained on imagiological vigilance.

Between 2009-2010 the patient initiated clinical manifestations of pain and limitation of shoulder mobilities. The x-ray showed an increased of the lesion. The new findings led to others imaging studies and a surgical biopsy. The histologic study was compatible to a desmoplastic fibroma.

In 2011, with 16 years old, the patient was submitted to an extended surgical excision of the lesion (the proximal cut was made in the "collum anatomicum") and subsequent vascularized fibular bone-grafting, and osteosynthesis with Philos plate.

**Results:** The final histologic findings described an Aneurysmatic Osseous Cyst arising in a Desmoplastic Fibroma. After surgery the patient presented clinical signs suggestive of transient radial nerve paralysis, but the neurovascular lesion reversed after some months of physiotherapy's treatment.

The patient's follow-up revealed an asymptomatic teenager with total fibular bone-grafting integration, without recurrence of the disease and with shoulder mobilities totally preserved.

**Conclusion:** Aneurysmal bone cyst arising in a desmoplastic fibroma led to a strange behavior and posed some difficulties in diagnosis. The aggressiveness of the aneurysmal cyst imposed an aggressive resection and a technically demanding reconstruction which succeeded and gave the patient an excellent functional outcome.

S. Kube<sup>1</sup>, D. Kosztyla<sup>1</sup>, I. Leuschner<sup>2</sup>, E. Hallmen<sup>1</sup>, T. Dantonello<sup>1</sup>, P. Winkler<sup>1</sup>, M. Greulich<sup>3</sup>, S. Bielack<sup>1</sup>, T. Klingebiel<sup>4</sup>, E. Koscielniak<sup>1</sup>

<sup>1</sup> Klinikum Stuttgart, Olghospital Stuttgart, Germany; <sup>2</sup>Dep. Pathology, Univ. of Kiel, Germany; <sup>3</sup>Diakonissenkrankenhaus, Stuttgart, Germany; <sup>4</sup>University Children's Hospital Frankfurt, Germany

**Introduction:** Malignant fibrous histiocytoma (MFH) was formerly regarded as a distinct fibrohistiocytic tumor type. However, it is now a diagnosis of exclusion in the group of soft tissue sarcomas (STS) called undifferentiated pleomorphic sarcoma (UPS). The reason for this is an improvement in diagnostic techniques that revealed that some former "MFHs" belong to other groups of soft tissue tumors. Correspondingly, the frequency of the diagnosis decreased enormously in adult soft tissue sarcomas. Due to its rarity, little is known about pediatric MFH/UPS.

**Materials and Methods:** 4736 patients < 21 years have been registered with the Cooperative Soft Tissue Sarcoma Study Group (CWS) between 1981 and November 2011. Sixty-seven patients were registered under the collective term "MFH" or UPS. A review of the pathology reports revealed that only 27 patients were diagnosed as MFH/UPS, while 25 were diagnosed as angiomatoid fibrous histiocytomas, 11 as benign or intermediate fibrohistiocytic tumors, two as myxofibrosarcomas and two as unclear lesions. Of the 27 MFH, nine patients had to be excluded from the analysis because of having bone MFH, missing reference pathology or missing source documents to re-review the pathology report. Of the remaining 18 patients, 8 patients were diagnosed between 1981 and 1990, 5 pts between 1991 and 2000, 4 pts between 2001 and 2010, and 1 patient since 2011. Thirteen of the 18 patients were further analyzed, while 5 patients with registration at the time of recurrence or loss to follow-up less than 5 years were excluded.

**Results:** Median age at diagnosis was 11 years (min 1.4y – max 18.5y). Tumor sites were extremities (n=8), trunk (n=3) and parameningeal site (n=2). Tumor was completely resected in five patients initially (IRS I). They are all alive after 0.7 – 8 years. Gross resection with microscopic residuals was seen in five patients. Four of them received radiochemotherapy, one only chemotherapy. One of the patients relapsed locally after 1.3 years and is alive after more than 10 years now. The one patient who did not receive radiotherapy was never in complete remission and died of progressive disease of a parameningeal MFH rapidly (OS 2 months). The two patients with IRS III received chemotherapy and second look surgery. One of the two patients developed metastatic disease (pulmonary) shortly after complete remission. He died within one year after diagnosis. The other patient is in complete remission for the follow-up period of 6 years. Only one patient presented with lymphatic metastatic disease at the time of diagnosis (IRS IV). He is in complete remission after multimodal therapy for the follow-up period of more than 12 years. 11 of 13 patients are alive with a median follow-up of 7.6 years (min 0.7y – max 12.9y).

**Conclusion:** The analysis of the pathology reports of pediatric patients registered within the CWS under the collective term MFH revealed a decrease in frequency of the diagnosis MFH over time. The general doubt in the diagnosis of MFH is thus reflected in our pediatric patient population. Interestingly, the decrease is most noticeable after the publication of C. Fletcher's "Pleomorphic Malignant Fibrous Histiocytoma: Fact or Fiction" in 1992. In context of multimodal therapy, primary complete resection seems not to be the only condition for survival, since other patients in our series have a nearly equal prognosis. Retrospective reevaluation of MFHs by reference pathology with current methods is indicated for MFHs diagnosed before ~1992 for further analysis regarding this patient group and resulting therapy advice. Genetic characteristics of UPS might even bring more insight into the pathogenesis and allow for specific therapy. Nonetheless, pediatric oncologists have to make decisions in current patients with UPS despite the uncertainty that results from the pooling of a retrospectively diverse group of pleomorphic sarcomas. The CWS-Guidance recommends therefore to treat these patients as other Non-RMS-like STS. Interestingly, the diagnosis of MFH is still accepted in the bone. Further analysis – pathologically and clinically – should be performed to investigate the differences between bone MFH and soft tissue UPS.

Pedro Santos Leite, Daniel Esteves Soares, Luciana Leite, Vânia Oliveira, Luís Costa, Pedro Cardoso

Department of Orthopaedics - Centro Hospitalar do Porto - Hospital de Santo António - Oporto, Portugal - [www.chporto.pt](http://www.chporto.pt)

**Objectives:** This paper reports a case of rib tumor in a 19-year-old male, discovered incidentally, which gave the false impression of aggressive behavior.

**Materials and Methods:** The authors present the case of a 19-year-old male, with no history of trauma, with a right chest wall lesion incidentally discovered during the investigation of a respiratory infection. Chest computed tomography showed localized expansive growth of the tumor, measuring 9,0 x 3,5 cm, centered in the right seventh rib, destroying it partially, with "sunray" periosteal reaction. Magnetic resonance imaging revealed low signal on T<sub>1</sub>-weighted images and a slightly high signal on T<sub>2</sub>-weighted images. A bone scan did not detect any other lesions. We performed a needle biopsy which revealed hemangioma of the rib. The patient underwent resection of the right seventh rib and reconstruction of the chest wall defect. He had an uneventful postoperative course. The definitive pathological diagnosis was cavernous hemangioma. There has been no evidence of recurrence after a 6-month follow-up.

**Discussion:** Bone hemangiomas are benign vascular tumors, extremely rare in the ribs. Most of the patients are asymptomatic and the lesion is discovered incidentally as in the case described. Because more than half of primary rib tumors are malignant, accurate diagnosis is imperative. It is challenging in the preoperative period. In this particular case we used needle biopsy.

**Conclusions:** The diagnosis of hemangioma should be considered in cases of an asymptomatic expansile rib lesion, although, not infrequently, radiographic findings can suggest malignant characteristics. A biopsy or resection may be required to establish the diagnosis. Surgical excision of the rib is the treatment of choice.

## INTRA OSSEOUS SCHWANNOMA OF THE TIBIA; CASES AND PATHOLOGICAL DISCUSSION

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*Cosker T, Gibbons M, Bayliss L, Takeshi T, Athanasou N, Whitwell D, Gibbons C L M*

*Nuffield Orthopaedic Centre, Oxford, UK*

**INTRODUCTION:** Schwannomas are benign tumours of the nervous system which originate from the neural sheath. They are usually seen as single, encapsulated, subcutaneous tumours in an otherwise normal individual. They can be found in the peripheral nervous system and have been reported in the brachial and lumbo-sacral plexus, nerves originating from the spinal roots and in any of the major named peripheral nerves. Schwannomas occur rarely in bone because sensory fibres and their associated Schwann cell rarely traverse bone during their normal anatomical course.

**CASE SERIES DISCUSSION:** Schwannoma of bone is an inherently rare condition with only around one hundred cases described in the English literature. Two cases are discussed here. Surgical resection and tibia diaphyseal reconstruction was undertaken and was curative in both cases with a good functional outcome both in terms of the Oxford Disability Score and TESS scores. Neither patient has demonstrated any evidence of recurrence. The genetic basis of this condition is becoming increasingly well understood and will also be presented in the meeting.



*Branford White HA, Bayliss L, Cosker T, Giele H, Critchley P, Whitwell D, Gibbons CLM.*

*Submitted by The Oxford Sarcoma Service, Oxford, UK*

**Introduction:** Primary soft tissue sarcomas of the extremities are uncommon. Many such lesions will present to specialists in other clinics such as specialist Hand or Foot and Ankle clinics. Many are of a small size at presentation and may appear to be alternate, more common pathology.

**Methods:** We collected data from all those patients with acral soft tissues sarcomas and referred to the Oxford Sarcoma Service over a thirteen year period from 1997 – 2010. Data were collected regarding the primary suspected diagnosis, the final diagnosis, the referral route and whether patients had undergone previous inadvertent excision.

**Results:** 43 patients were treated (28 foot, 15 hand tumours). The commonest histological subtype was synovial sarcoma in the foot group, and leiomyosarcoma in the hand group. 25 of the 43 patients had a lesion of less than 5cm at presentation. For those patients in whom a wide excision was performed 50% underwent complex plastic surgical reconstruction.

**Discussion:** This study shows that 30% of patients with acral tumours required further surgery due to previous inadequate / inadvertent excision. 5cm as a benchmark for specialist referral should not be applied to lesions in the hand or feet and we recommend the use of the “marble rule” i.e. any lesion the size of a marble should be referred urgently and no patient should undergo surgery without imaging.

# OCCULT INTRA ARTICULAR MYXOMA OF THE KNEE: A CASE REPORT.

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*Huseyin Botanlioglu, Rifat Erginer, Gokhan Kaynak, Muharrem Babacan, Atakan Karabiber, Mustafa Caliskan*

**Objectives:** Juxta articular myxomas (JAM) are rare benign tumors of the connective tissue which have high recurrence rate. JMA are occasionally seen in large joints, like knee joint. The differential diagnosis for such an intra- or periarticular mass should include ganglion cyst, synovial lipoma, lipoma arborescens, or pigmented or nonpigmented villonodular synovitis and even sarcomas. We present a case of intraarticular myxoma of the knee.

**Materials and Methods:** A 51 year-old patient presented with complaints of pain and swelling of the knee without a history of trauma. Physical examination of the knee was normal but Magnetic Resonance Imaging (MRI) revealed an intra-articular mass in of the knee. Preoperative diagnosis was unclear. Sarcomas, synovitis or ganglion cysts were considered as a differential diagnosis. Diagnostic arthroscopy were performed and the specimen revealed spindle cells and mesenchymal cells which had myxoid change. In our case, this lesion was hidden to medial patellofemoral joint and because of that palpation of the mass was difficult. The lesion was removed by marginal resection by open surgical procedure. The size of the lesion was 5x4x1,7 cm.

**Results:** Metastasis and recurrence was not noted follow-up.

**Conclusion:** The peak incidence of myxoma is between the 3rd and 5th decades of life. As in our patient, these lesions were slow-growing and well-circumscribed. Recent case, diagnosis of the lesion was confirmed with pathological examination and size of the lesion may be ranged from 0,6cm to 12cm. Gadolinium-MR imaging is important for the differential diagnosis. The tumor appears hyperintense on T-2, hypointense on T-1 on the MRI. Such lesions are characterized as multilobulated and bound within a capsular rim. JMA has a high recurrence rate but no metastasis noted and relationship with osteoarthritis of the concomitant joint have been reported. Occasionally juxta articular myxomas are found incidentally during knee or hip arthroplasty and diagnosed as a benign lesion. For the 23% of the cases diagnosis of sarcoma was considered or proved by the specimen. Juxtaarticular myxoma should to be considered in patients whom are presented with a painful restricted motion of the knee, Definitive diagnosis of these lesions are very important especially in patients whom are present with pain and swelling of the knee, because it can mimic sarcoma and can be misdiagnosed. It should be kept in mind that the lesion can hide joint.

Quattrini I,<sup>1</sup> Pazzaglia L,<sup>1</sup> Mosakhani N, Borze I,<sup>2</sup> Novello C,<sup>1</sup> Knuutila S,<sup>2</sup> Picci P,<sup>1</sup> and Benassi MS<sup>1</sup>

<sup>1</sup>Laboratory of Experimental Oncology -Istituto Ortopedico Rizzoli, Bologna-Italy

<sup>2</sup>Laboratory of Cytomolecular Genetics Research-Haartman Institute -University of Helsinki

**Background:** Giant Cell Tumor (GCT) is a benign bone tumor that has a relatively high local aggressiveness, while development of lung metastases is a rare event, occurring in 2%-5% of cases. MicroRNAs are approximately 22 nucleotide-long noncoding RNAs involved in several biological processes including development, differentiation and proliferation. Recent studies suggest that knowledge of miRNA expression profile in cancer may have substantial value for diagnostic and prognostic determinations as well as for possible therapeutic treatments. Our aim was to integrate mRNA and microRNA expression profile in GCT clinical specimens in order to identify a specific signature correlated to disease progression.

**Materials and Methods:** Using miRNA microarray, we analyzed miRNA profile in 10 GCT, from 5 metastatic and 5 non metastatic patients. Expression levels of selected miRNAs will be confirmed by Real time PCR in a larger cohort of tumors and the correlation between miRNA and mRNA expression data will be performed by bioinformatic tools.

**Results:** We found 12 miRNAs differentially expressed in metastatic and non-metastatic tumors. In particular let-7a\* and miR-513a-3p were exclusively expressed in metastatic tumors, while miR-1 and miR-136 were up-regulated in all non-metastatic tumors. The decreased level of *miR-136* in metastatic compared to non-metastatic GCTs was significantly confirmed by qRT-PCR ( $p=0.04$ ).

The correlation between miRNA and mRNA expression data revealed that NFIB gene, a progression-associated gene in cancer, is a potential target of *miR-136*.

**Conclusions:** Our data suggest that miR-136 expression could be relevant in the biological behaviour of GCT. Proteomic analysis are ongoing to assess the expression level of NIFB protein and expected downstream activated pathways.

# SOFT TISSUE SARCOMAS AND METASTASIS TO THE BONE: PROTEIN SIGNAL PATHWAY MAPPING IN THE METASTASIS MICROENVIRONMENT

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Conti A.<sup>1,2</sup>, Chiechi A.<sup>1,2</sup>, Novello C.<sup>1</sup>, Magagnoli G.<sup>1</sup>, Benassi M.S.<sup>1</sup>, Picci P.<sup>1</sup>, Liotta L.<sup>2</sup>, Espina V.<sup>2</sup>

1. *Laboratory di Experimental Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy*
2. *Center for Applied Proteomic and Molecular Medicine, George Mason University, Manassas, Virginia*

**Introduction:** Soft tissue sarcomas (STS) are a heterogeneous group of benign and malignant diseases. More than 99% of these tumors are benign. For the 1% of STS that are malignant, 7-10% are from pediatric patients. The rarity of these tumors makes the diagnosis, grading and therapy selection difficult.

Proteomic molecular profiling can be used to identify pathways or specific proteins as potential drug targets or molecules useful for stratification of patients with STS and for the identification of patients with poor prognosis.

We used Reverse phase protein arrays (RPMA) to analyze extracts of STS bone metastases and normal counterpart bone. We measured proteins involved in bone metabolism, tumor-host interaction, hormone response, growth-proliferation, stress-inflammation and adhesive-cytoskeletal pathways.

The aim of this study was to identify prognostic biomarkers and potential targets for molecular targeted therapies.

**Materials and Methods:** 35 fresh frozen bone metastasis samples from patients diagnosed with primary STS, 10 primary STS specimens, and 10 adjacent normal tissues, were completely homogenized using CryoPrep™ and Adaptative Focus Acoustic™ (AFA™) technology by Covaris, with very good protein extraction efficiency. The expression of 50 proteins belonging to multiple signal transduction pathways was quantified by RPMA.

**Results:** In the first phase of this study we evaluated the expression of 23 key proteins involved in bone metabolism, tumor-host interaction, hormone response, growth-proliferation, stress-inflammation and adhesive-cytoskeletal pathways. Altered expression ( $p < 0.05$ ) was found for proteins involved in bone metabolism, matrix breakdown, growth-proliferation and hormone and inflammation response. In particular, differences between the group of normal counterpart tissues and primary STS were found in the levels of Ezrin Y353 and RANK; Her3 Y1229, MMP11, mTOR S2448, RANK between primary tumors and bone metastasis; Ezrin Y353, MMP14, mTOR S2448, PERK, Serotonin, TNFR1 between adjacent normal and bone metastasis.

**Conclusions:** This pilot study demonstrates that quantitative proteomic analysis can be readily conducted on sarcoma bone metastasis. For this underpowered study differences were noted in bone and connective tissue remodeling pathways between primary tumors, metastasis and benign bone. An expansion of this pilot series to a larger study set may provide strategies to improve diagnosis, grading and therapy for STS.

# TWO-STAGE REVISIONS FOR INFECTION – WHAT ARE THE LONG-TERM RESULTS IN MASSIVE ENDOPROTHESES?

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H. Wafa, R.J. Grimer, V. Neelapala, S.R. Carter, R.M. Tillman, A. Abudu, L. Jeys

The Royal Orthopaedic Hospital Oncology Service, Birmingham, United Kingdom.

Corresponding author: Hazem Wafa email: hazem.wafa@nhs.net

**Objectives:** This study evaluates the long term outcomes of two-stage revisions of infected endoprostheses, in particular function, re-infection, and amputation.

**Introduction:** Infection around an endoprosthesis implanted for bone tumour is a disaster for the patient. It is costly to treat and the results are uncertain. Two-stage revision seems to be the most successful way of resolving infection around an endoprosthesis, with reported success rates of 70-85%.

**Material and Methods:** All patients who had undergone a two stage revision for infection of a massive endoprosthesis for a bone tumour were identified from a prospective database. The patients were treated by removal of the implant and all infected material, insertion of an antibiotic spacer (usually Gentamicin and Vancomycin), intravenous antibiotics for a minimum of 4 weeks then aspiration followed by reimplantation if the aspirate was negative. 84 patients had adequate follow up and were included in the study of whom 57 were male and 27 female. The patients had a mean age of 23.1 years (range, 2-70 years) at the time of diagnosis of the neoplasm and 28.8 years (range, 10-71 years) at the time of infection. Endoprosthetic replacements were of the distal femur (44), proximal tibia (28), proximal femur (7), proximal humerus (2) and three others. Soft tissue coverage of the prosthesis was provided by local pedicled flaps in 9 patients and by free flaps in six.

**Results:** Mean follow up was 6.9 years (range, 0.5-21.8 years) from the date of the second stage of prosthetic revision. The 84 patients had an average of 3.4 operations before the development of infection. The mean time to infection was 5.5 yrs from original insertion of the first prosthesis. In 49 patients (58.3%), prerioprosthesis infection was detected within 6 months from the last surgical procedure. The most common pathogenic organisms were coagulase-negative staphylococci (61.9%) and staphylococcus aureus (16.7%). The overall success rate in controlling infection was 72% at 1 year and 65% at 5 and 10 yrs. Fourteen patients (16.7%) ended up with amputations due to uncontrolled periprosthetic infections. 26 patients (30.1%) had positive cultures of the samples taken at the time of the 2<sup>nd</sup> stage of the prosthetic revision despite negative cultures of the preoperative aspiration. 11 of these 26 patients (42%) eventually had an amputation compared with 5% if the cultures were negative ( $p=0.0001$ ).

Twenty-four patients have received silver-enhanced implants at the time of revision surgery while the remaining sixty patients had conventional endoprostheses. Eight of the 10 patients (80%) with positive cultures at the second stage surgery and who received silver implants had no clinical evidence of infection at the time of their latest follow-up. Fourteen of those sixteen patients (87.5%) with positive 2<sup>nd</sup> stage cultures and who received conventional implants had clinical relapse of infection. The mean MSTS score was 78.6%.

**Conclusions:** Infection is the most serious complication of endoprosthetic replacement in limb salvage surgery. The risk of amputation is particularly high in those patients with positive cultures at second-stage surgery. Silver-enhanced implants maybe of value in this subgroup of patients.

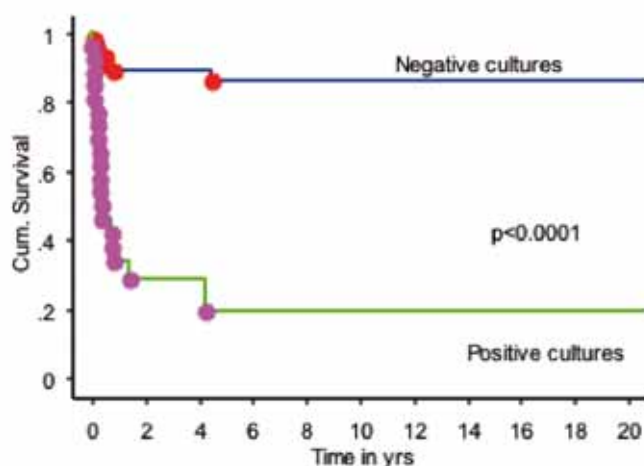


Fig 1. Survivorship of patients without reinfection after a two stage revision split by whether they had a positive culture result or not at the second stage procedure.

# SURGICAL PROCEDURE “IN SITU PREPARATION” FOR SARCOMA OF LIMB IN CLOSE PROXIMITY TO MAJOR NEUROVASCULAR STRUCTURES.

013

*Dept. of Orthopaedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan*

*Naoto Oebisu, Manabu Hoshi, Jun Takada, Makoto Ieguchi, Susumu Taguchi, Hiroaki Nakamura*

**Background:** When soft-tissue sarcoma is excised, the surgical margin according to the histological grading is important. When soft-tissue sarcomas occur near neurovascular structures, only preoperative images cannot always reveal the accurate relationship between the tumor and these structures. Previously, the surgical method, namely “In Situ Preparation”, was introduced in 2002. This method enables the preparation of neurovascular bundles and the intraoperative evaluation of the surgical margin without contamination by tumor cells and then additional procedures, including alcohol soaking, and distilled water soaking of the preserved neurovascular bundle can also be performed to preserve the continuity of vessels.

**Method:** Between January 2006 and October 2009, ISP was applied to 8 patients (5 women and 3 men) with soft tissue sarcomas of limbs in close proximity to major neurovascular structures.. The average age is 60.5 years old (from 35 to 78 years old) and average follow up period is 319 days. The pathological diagnosis confirmed myxoid liposarcoma in 2, pleomorphic liposarcoma in 4, myxoinflammatory fibroblastic sarcoma in 1, and phosphaturic mesenchymal tumor in 1. The tumors occurred in thigh in 5, lower extremities in 1, and forearms in 2.

**Result:** Complete local controls were achieved in all patients at last follow-up. Oncological outcomes were DOD in 5 patients, and CDF in 3. No complications, including nerve palsy, embolism, and infection were observed,

**Conclusion:** ISP enabled intraoperative evaluation of the surgical margin without contamination, and preserved limb functions without unnecessary sacrifice.

# CUSTOM MADE PROSTHESIS OF DISTAL TIBIA AND ANKLE AFTER RESECTION FOR BONE TUMORS: REPORT OF TWO CASES.

024

*\*N.Salducca, °V.Ippolito, \*U. Prencipe, \*L. Favale, \*C. Zoccali, \*G. Marolda, \*R. Biagini*

*\*S.C. ORTOPEDIA IFO- ISTITUTO REGINA ELENA – ROMA – ITALY*

*° REP. ORTOPEDIA CIVIL HOSPITAL – BRESCIA – ITALY*

**Objectives:** Authors present two cases of patients treated at two different institutions with a custom made prosthesis of distal tibia and ankle after resection for bone tumors.

**Materials and Methods:** At the Civil Hospital of Brescia and IFO-Istituto Regina Elena of Rome two patients were treated with a Custom Made Prosthesis of Distal Tibia and Ankle after resection for bone tumors. Diagnosis were osteosarcoma (one case) and Ewing's sarcoma (one case). The prosthetic stem proximally was fixed in both cases by press-fit and distally in one case by press-fit and one by cementation. Functional analyses (according to the MSTS) was performed.

**Results:** Functional results were excellent in both cases: we observed a good active movement without lameness when walking. The MSTS score was more than 80%. We haven't observed complications or local recurrences or metastases.

**Conclusions:** Implantcast prosthesis of distal tibia is an excellent way to improve ankle function after resection for bone tumors and it is an important way to avoid rigidity and abnormal deambulation especially in young adult patients.



Paul L<sup>1</sup>, Docquier PL<sup>1</sup>, Cartiaux O<sup>1,2</sup>, Delloye C<sup>1</sup>, Banse X<sup>1</sup>.

<sup>1</sup> Computer Assisted and Robotic Surgery (UCL/CARS). Avenue Mounier, 53 Tour Pasteur +4. 1200 Brussels. Belgium.

<sup>2</sup> Ecole Polytechnique de Montréal. Department of Mechanical Engineering. 6079, Station centre-ville, Montréal, Canada H3C3A7.

**Objectives:** Bone tumor often requires a surgical resection of the tumor. Some tools have been developed to assist the surgeon during the pre-operative and intra-operative steps. The planning leads to accurately define the extension of the tumor, plan resection trajectories (including a safe margin) and select an optimal allograft (if required). The transfer into the operative room has been achieved using a specifically modified navigation system. Since few months, patient-specific devices have come up to guide the saw blade during bone cuttings, such as total knee arthroplasty. This technology has been transposed to resect bone tumors. An experimental study has been led on sawbones to assess the accuracy of the method and compare the results with the one of a previous experiment using conventional and navigated methods. We present the preliminary results of this new experiment and some clinical cases that have already benefited from the technique.

**Materials and methods:** The pre-operative planning consists in localizing the tumor, positioning cutting planes around the tumor adding a user-defined safe margin, and, if required, selecting an allograft. Once these steps have been achieved, patient-specific guides are built using a Computer Assisted Design software (CAD). The surgeon checks whether their shape is consistent with the surgical approach and the available bone surface. A rapid prototyping machine is used to manufacture the devices. During the surgery, the guide is positioned onto the bone surface and temporarily fixed using K-Wire.

These stages have been used to perform a virtual tumor resection located on a pelvic sawbone. Specific guides have been manufactured, and provided to operators who were asked to resect the bone tumor. The safe margin and the position of the cutting plane (location; ISO standard for evaluating the error between two planes) have been used to quantify the accuracy of the method. Six bone tumors have already been resected using this technique. An additional guide is also provided when an allograft is used, to optimally adjust the allograft

**Results:** To date, the accuracy of the resection using the specific guide is excellent. The obtained safe margin is very closed to the target 10 millimeters (average error of 0.63 millimeters). The error between target and actual planes (e.g. location) is 1.34 millimeters.

The clinical cases have systematically shown a tumor-free resection. The reconstructions using an allograft have shown an excellent contact at osteotomy sites, and thus a satisfying reconstruction of the anatomy.

**Conclusions:** The experiment has shown that patient-specific guides can be trusted for bone tumor resections. They provide a high accuracy and a high repeatability of osteotomies. Clinical cases has proven the feasibility of the technique and shown some advantages. They are quick and straightforward to use, no additional material is required, biomaterial is certified for clinical use. Pre-operatively, the surgeon has to provide some guidelines to the engineer for creating smart guides (desired safe margin, diameter of K-Wires, available bone surface, saw blade thickness). He receives them ready to be sterilized and used during the surgery. We think this technique has a high added value and is very promising for surgical oncology.

*N.N.Blokhin Russian Cancer Research Center , Russian Academy of Medical Sciences, Moscow 2012  
VA Sokolovskiy, PS Sergeev , AA Babalaev, AV Sokolovskiy, MN Kubirov, MD Aliev*

**Materials and Methods:** During the period from 1979 to 2010 year in RCRC 1181 primary operations performed in the volume of replacement of large joints of various locations, among the interventions were resected bones forming the shoulder (n = 134), elbow (n = 10), hip (n = 167), knee (n = 786), and ankle joints (n = 8). Endoprosthesis with total hip replacement n = 50, humerus, n = 16, tibia n = 1. The defect is replaced by the individual and modular endoprosthesis. The defeat of the bones were due to primary tumors in 92% of patients, metastatic - 8%. The average age of patients was  $28 \pm 14$  years (from 10 to 80 years), 53.5% were men, women - 46.5%. Osteosarcoma predominated (46%) in the remaining cases were diagnosed chondrosarcoma (10%), Ewing's sarcoma (5%), giant cell tumor (14%), other morphological forms consisted of 25%.

**Results:** The average follow-up was 10 years old. Overall survival is 61%. The recurrence rate was 12%. Among the complications of infection are marked (11%), instability of the prosthesis (13.7%). The prosthesis survival corresponded to 54%. Functional evaluation of MSTS score was 70% for operations on the shoulder joint endoprosthesis, 80% - for the hip. MSTS after arthroplasty of the femur consistent 58% - with its total replacement and 92% - of the distal resection, evaluation after resection of the proximal tibia - 75% and 72% at the distal.

**Conclusion:** Endoprosthetic reconstruction gave satisfying functional and oncological results and low rate of complications in most patients after long-term survival. Limb salvage surgery is the gold standard of modern onco-orthopedics

# DISASTROUS FAILURE OF THE HINGED TIBIAL INSERT OF A ROTATING HINGE DESIGN: A RETROSPECTIVE DATA ANALYSIS

031

Joerg Friesenbichler<sup>1</sup>, Ran Schwarzkopf<sup>2</sup>, Patrick Sadoghi<sup>1</sup>, Scott E. Marwin<sup>2</sup>, Mathias Glehr<sup>1</sup>, Werner Maurer-Ertl<sup>1</sup>, Ulrike Pirker-Frühauf<sup>1</sup>, Andreas Leithner<sup>1</sup>.

<sup>1</sup>Department of Orthopaedic Surgery, Medical University of Graz, Graz, Austria.

<sup>2</sup>Department of Orthopaedic Surgery, NYU Hospital of Joint Disease, New York, NY, USA.

**Purpose:** Rotating hinge knee prostheses are used for knee reconstruction following resection of malignant bone tumours because these prostheses provide inherent stability. Yoke fractures of the hinged tibial insert of modern generation rotating hinge devices are a matter of continued concern. The aim of the study was to describe incidence and management of yoke fractures of the hinged tibial insert of a modern rotating hinge design.

**Materials & Methods:** Retrospective data analysis of two institutions identified 40 patients who were treated with a Limb Preservation System (LPS™, DePuy, Warsaw, IN) for distal femoral reconstruction following wide tumour resection. Implant survival to prosthetic complications was calculated according to Kaplan-Meier.

**Results:** Out of the group of 40 patients, four fractures of the metal yoke occurred in four cases (failure rate: 10%). Furthermore, a second fracture re-occurred in two patients. The overall revision-free prosthetic survival was 57% at 38 months, while prosthetic survival until yoke fracture was 86% at 38 months.

**Conclusion:** Handling yoke fractures as mechanical complication includes; replacing the hinged insert, stabilization of the joint and joint line height preservation in order to decrease the cantilever effect at the insert-base plate interface. Nevertheless, a failure rate of 10% for this specific complication is not acceptable and as a salvage option, we recommend the exchange of the prosthesis to another rotating hinge design.

SEGURA, Florencio – MD, PhD – PROFESSOR IN ORTHOPAEDICS

SEGURA, Florencio Pablo

SEGURA Facundo

ZECCHINI, Lorena

CARPINELLA, Pablo

MUSCULOSKELETAL TUMOR UNIT

UNIVERSIDAD NACIONAL DE CORDOBA

CORDOBA –ARGENTINA

**INTRODUCTION:** The proximal humerus and femur have serious inconveniences for their reconstruction with massive endoprosthesis after the resection of high grade bone sarcoma. The compromise of the soft tissues which function as joint stabilizers, due to the pathology in itself or due to surgery, determines the need to use a technical resource which prevents post-surgical instability.

**MATERIAL AND METHOD:** A retrospective evaluation was done of 8 patients treated between 2000 and 2009 with non conventional endoprosthesis with a dracon covering to anchorage the soft parts after wide resection of malignant tumoral lesions. Six of these cases corresponded to lesions of the proximal humerus and two of them to lesions of the proximal femur. The base diagnosis corresponded in 5 cases to an osteosarcoma, in 2 cases to a giant cell tumor, and in 1 of them to thyroid carcinoma metastasis.

**OUTCOMES:** The average follow up time consisted of 5 years and 6 months. The MSTS/ISOLS score was 70 % of the normal function for the 6 proximal humerus cases and 80% of the normal function for the 2 femur proximal cases. No episodes of acute instability were registered. Out of the 6 proximal humerus cases, 3 present a subluxation of the prosthetic head of 2 to 4 mm in its long term evolution.

**DISCUSSION:** The use of synthetics covering the prosthesis' surface constitutes a valid choice to avoid post surgical instability in large oncologic resections of the proximal femur or humerus. Dacron® is an attractive material not only for its biological properties and mechanics, but also for its low cost and availability.

**KEY WORDS:** Endoprosthesis. High grade bone sarcoma. Instability. Ligamentoplasty. Dracon.

# RECONSTRUCTION IN ONCOLOGICAL RESECTIONS OF THE PROXIMAL HUMERUS

041

*SEGURA, Florencio – MD, PhD – PROF. IN ORTHOPAEDICS - SURGEON IN CHIEF*

*SEGURA, Pablo*

*SEGURA, Facundo*

*ZECCHINI, Lorena*

*CARPINELLA, Pablo*

*MUSCULOSKELETAL TUMOR UNIT*

*UNIVERSIDAD NACIONAL DE CORDOBA*

*CORDOBA –ARGENTINA*

**INTRODUCTION:** The proximal humerus is a challenge for its reconstruction after the resection of bone sarcomas. The compromise of soft tissues which function as joint stabilizers, due to the pathology in it or due to the surgery, determines the need to use different types of technical resources.

**MATERIAL AND METHOD:** A retrospective evaluation of 16 patients treated between 2000 and 2009 with resections of the proximal humerus is presented.

**OUTCOMES:** The average time of follow up was 5 years and 6 months. The MSTS/ISOLS was 70% of the normal function.

N.Salducca, C. Zoccali, L. Favale, U. Prencipe, G. Marolda, G. Teori, F. Erba, R. Biagini

IFO- ISTITUTO REGINA ELENA – ROMA - ITALY

**Objectives:** Authors present 4 cases of patients treated with a reverse shoulder prosthesis after resection for bone tumors of proximal humerus.

**Materials and Methods:** At the IFO-Istituto Regina Elena S.C. ORTOPEDIA, from Jun. 2009 to Dic. 2011, 4 patients were treated with a reverse shoulder prosthesis (Mutars® Implantcast) after a Malawer type Ia or Ib resection for bone tumors. In three cases they were female (75%). Diagnosis were osteosarcoma (two cases), GCT (one case) and breast solitary methastasis (one case). The prosthetic stem was fixed in 2 cases by cementation and in two cases by press-fit.

Functional analyses (according to the MSTS) was performed.

**Results:** Functional results were good or excellent in all the cases: we observed a minimum active abduction of 65 degrees, reaching 90 degrees or more in all the patients. The mean MSTS score was more than 80%. We haven't observed complications or local recurrences or metastases.

**Conclusions:** Reverse shoulder prosthesis is an excellent way to improve shoulder function after resection for bone tumors of proximal humerus especially when you can avoid the delthoid muscle and axillari (circumflex) nerve resection.

# FUNCTIONAL OUTCOMES AFTER SCAPULECTOMY FOR MALIGNANT TUMORS IN THE SHOULDER GIRDLE

057

Suguru Nakamura, Takaaki Kuroda, Masanari Aono, Kenichi Kazuki

Department of Orthopaedic Surgery, Osaka-City General Hospital - Tomoaki Suzuka

**Introduction:** Treatment and reconstruction for malignant tumors of the shoulder girdle associated with postoperative functional outcome of the entire upper limb.

**Purpose:** The purpose of this study was to assess the functional outcomes after total scapulectomy.

**Patients and Methods:** We describe the cases of five patients (three men and two women) who underwent reconstructive surgery for malignant tumors of the scapula and the proximal humerus between February 2008 and July 2012. The age of the patients ranged from 67 to 74 years. Pre-operative histopathological diagnosis revealed rhabdomyosarcoma (one patient), extraskeletal myxoid chondrosarcoma (one), recurrence of malignant fibrous histiocytoma (one), and metastatic bone tumors of the adrenal and thyroid (two). Scapular resections were performed according to the surgical classification of shoulder girdle resections described by Malawer. Four patients underwent subtotal scapulectomy surgery. In three of these patients (Type IIa resection), the neck of the scapula and the glenoid were retained, whereas in the other patient (Type IIb) only the glenoid was retained. The remaining patient (Type VI) underwent total scapulectomy and amputation of the upper limb. Functional outcome was evaluated using the Enneking score.

**Results:** The patients received an average follow-up time of 24 months (range 5~47 months).

In all cases, there was no local recurrence. In two patients, metastasis occurred during the follow-up period, whereas the other patients remained disease-free after surgery.

The mean Enneking score in Type IIa patients was 84.7% (80%–87%), whereas the score for the Type IIb patient was 67%, and that for the Type VI patient was 16%.

**Discussion:** Recently, it has been reported in some articles that shoulder girdle function decreases dramatically following total scapulectomy. Other articles suggest that residual shoulder function after surgery depends on both retention of the glenoid and reconstruction of the muscle around the shoulder girdle. We agree that, if tumor-free, every effort should be made to preserve the glenoid.

In our study, all three patients who underwent a Type IIa resection had excellent functional outcomes, compared with Type IIb and Type VI patients. We found that upper limb movement is greater with retention of not only the glenoid but also the abductor mechanism within the upper part of the scapula. We consider that this is a promising technique that allows for future range of motion, particularly abduction movement of the shoulder joint.



Vyrva Oleg, Burlaka Victor, Karpinsky Mikhailo, Mikhanovsky Dmitro

Sytenko Institute of Spine and Joint Pathology, Kharkiv, Ukraine

**Introduction:** The one of the most common complications of tumor prosthesis replacements (TPR) are prosthetic stem fractures (1,6-18,2% of all number TPR) and periprosthetic fractures (0,7-8,1% of all number complications). These complications are related uneven load on the different elements of the “endoprosthesis – bone” system. Maximal peak of load is on base of the endoprosthesis intramedullary stem. The main goal of this investigation was to create mathematical models for stress load calculation of different external and internal fixing prosthesis parts and to compare stability of fixation for different types of bone forms.

**Materials and methods:** Using the finite elements method we have studied of mechanical properties of the “endoprosthesis – bone” system. We used a model of radius bone. For this research mathematical model of the system “endoprosthesis – radius” we studied three types of radius bone with round, oval and triangle forms for bone. Also we studied biplate, triplate and cylindrical tube form of extracortical fixation of the endoprosthesis respectively. Study was performed with two types of loading: tension and bend. Strength of load was 100 N that corresponds to usually everyday loading of the forearm.

**Results:** *Tension (stretch) loading.* Maximal tensions were in the proximal part of the stem, on surfaces of the bone canal in places of contact with stem, on external surface of bone in places of contact with extracortical plates and in extracortical plates. Strength of loading was 1,5 MPa in the system with the round form of the bone and cylindrical extracortical tube of the endoprosthesis. Strength of loading was 1,3 MPa in the system with the oval form of the bone and biplate extracortical fixation. Strength of loading was 1,1 MPa in the system with the triangle form of the bone and triplate extracortical fixation. *Bending loading.* Maximal tensions were on external surface of bone in places of contact with extracortical plates and in extracortical plates. Tensions were less on upper and low surfaces of the stem and on surfaces of the bone canal in places of contact with stem. Maximal strength of loading was 42,0 MPa in external parts of the system with the round form of the bone and cylindrical extracortical tube of the endoprosthesis and 35,0 MPa in internal parts of the same system. Maximal strength of loading was 44,5 MPa in external parts of the system with the oval form of the bone and biplate extracortical fixation of the endoprosthesis and 32,0 MPa in internal parts of the same system. Maximal strength of loading was 38,0 MPa in external parts of the system with the triangle form of the bone and triplate extracortical fixation of the endoprosthesis and 30,0 MPa in internal parts of the same system.

**Conclusion:** Endoprostheses with combined type fixation have even load on all elements of connection. Endoprosthesis with triplate external fixation with bone of triangle form is most optimal system. Maximal tensions are in external parts of fixation devices of the same system. This system is most approximate to natural bone. These data and results are very useful for custom made and modular tumor prosthesis manufacturing.

## FEMUR METASTATIC DEFECTS REPLACEMENT DEPENDING ON THEIR LOCATION

062

Vyrva Oleg, Golovina Yanina, Malik Roman, Shevchenko Igor

Sytenko Institute of Spine and Joint Pathology,

Kharkiv, Ukraine

**Introduction:** According to the literature the lower limb bones are the common site of metastatic lesions (67%) and especially the femur (54%). Most metastases are lytic lesions. There is the high risk of development a pathological fractures for these lesions. At the same time, lost support ability of the affected limb and significantly decreases the patient's ability to self-service. Wide tumor resection and replacement of bone defects by different implants combined with bone cement (plates, intramedullary nails, endoprosthesis) are performed with solitary bone metastases of different localization. The fractures of the implants occur in some cases. The femur and the various options for replacement of post-resection defects depending on the localization of tumors in the bones were chosen for this study. The main goal of this investigation was to determine the most optimal replacing method of post-resection femur metadiaphysis defects for patients with solitary metastases.

**Materials and Methods:** The custom made titanium construction to replace post-resection distal femur metadiaphysis defects was designed. The design consists of the L - shaped plate, cylindrical module, intramedullary stem, which are joined together by screws. The finite element method was used in this study. The femur with simulating defects in different locations was the base model. The study included 4 models of the femur with various types of the replacement post-resection defects: a model with partial distal femur defect which was replaced by L-shaped plate and the bone cement; L-shaped plate, bone cement and two intramedullary nails, metal construction and a model with a partial distal femur defect which was replaced by intramedullary nail and bone cement. Stress-deform conditions were studied at three main types of load: axial, flexion, rotation.

### **Results:**

- maximum stresses during work of construction which consists of L-shaped plate and bone cement arises in the "implants-bone" contact zone of distal femur;
- load peak is localized in the contact zone "implants-bone" in proximal femur during work of construction which consists of intramedullary nail and bone cement.

**Conclusions:** The lowest stresses was observed in the "implant-bone" contact zone using bone cement, L-shaped plate and intramedullary rods, as well as the use of the proposed construction for replace defects in the metadiaphysis of distal femur. Also modular endoprosthesis replacement is method of choice for replacement of proximal femur defect according to high risk of implant fracture using intramedullary nail and cementation this part of femur bone.

Khurshid G.Abdikarimov

National Oncology Research Centre, Tashkent, Uzbekistan

**Aim:** Analysis of surgical treatment results of tumor in the soft tissue in brachial girdle.

**Materials and methods:** Analysis of surgical treatment results of 83 patients with tumor of soft tissue in brachial girdle was performed. Men - 44, women- 39. Patients age was vibrated from 15 till 76, in average - 38, 8 . In 50 cases tumor was localized in 2 shoulders, 10 – scapular, 9 –suprascapular, 8 – axillary, 3 – supraclavicular and 3 – clavicular regions. By histological structure 43 patients with fibro sarcoma were prevailed, in others rhabdomyosarcoma - 12, synovial sarcoma - 9, angiosarcoma - 7, unclassified tumors – 6, lip sarcoma – 2, mix sarcoma – 1 and desmoids tumor - 3 were observed. In 68 cases organ conserving operations – wide excision of tumor in the volume of muscular- facial membrane - 56, wide excision of tumor with lymph dissection of axillary lymph nodes - 4, combined operations - 8 (excision of tumor with edge resection of brachial girdle - 2, with resection of ribs – 2, with resection of scapula – 1, with scapula ectomy – 2 and in 1 –excision of tumor with resection and autoplasic of axillary artery). In 15 cases crippling operations - interscapular-thoracic amputation -13, exarticulation on the level of brachial joint- 2.

**Results:** In the period of observation 10 – 180 months, in 26 patients (31, 3%) appeared relapse, in 8 patients were some relapses in the course of disease. In (37, 3%) patients – remote metastasis. Remote metastasis prevailed in the group of patients after crippling operations.

**Conclusion:** The basic method of treatment patients with sarcoma of soft tissue remains –surgical. Optimal value of operative intervention is wide excision of tumor in the volume of muscular-facial membrane. Combined operations were shown in spreading of process on brachial girdle bones. Crippling operations were shown in large volume of tumor with damage of some anatomical structure, involving the great vessels and nerve, and major destruction of brachial bones.

## TREATMENT RESULTS OF MALIGNANT TUMOR OF SOFT TISSUE IN EXTREMITIES.

075

Khurshid G.Abdikarimov, Rasul R.Davletov, Mirza A.Gafur-Akhunov, Djamila Sh.Polatova, Ulugbek F.Islamov, Fahriddin E.Nasritdinov, Kamol Iskandarov

National Oncology Research Centre, Tashkent, Uzbekistan

**Aim:** To study the efficacy of treatment methods patients with malignant tumors of soft tissue in extremities.

**Materials and methods:** Analysis of surgical and combined methods of treatment results was performed in 144 patients with malignant tumors of soft tissue in extremities. Men were 100 (69, 4%), women - 44 (30, 6%), aged from 16 till 82, at an average - 40, 5. Size of tumors by these instrumental methods of investigation (MRT, CT, USD) was from 5 till 22 sm in maximal measurement. In all patients were performed morphological verification of diagnosis by incisional biopsy with trepanation and open method. By histological structure of tumor : fibro sarcoma in 99 (68,7 %) patients, rhabdomyosarcoma - 18 (12,5%), synovial sarcoma - 9 (6,5%), angiosarcoma - 7 (4,9%), fibro mix sarcoma- 6 (4,2%), neurosarcoma - 2 (1,4%), malignant fibrous histiocyoma - 2 (1,4%), 1 (0,7%) – lip sarcoma were determined. In 104(72, 2%) patients with high degree of malignant tumor (G3, 4) and with size of more than 5 sm was performed combined treatment, including no adjuvant chemo or beam therapy. Pure surgical therapy was performed in 40 (37, 8%) patients with low degree of malignancy. In 112 cases (77, 8%) conservative, in 32 (22, 2 %) – crippling operations were performed (in the volume of amputation, disarticulation, hemipelvectomy, interscapular–thoracic amputation).

**Results:** Relapse of tumor appeared in 19 (18,3 %) patients from 6 months to 3 years old in the group of combined treatment in the term of observation, remote metastasis in 18 (17,3 %) ,in the group of surgical treatment in 4 (10 %) – relapse and in 14 (35%) - metastasis were observed.

**Conclusion:** Combined method is the method of choice in treatment of patients with sarcoma of soft tissue in extremities with high degree malignancy, effect from no adjuvant component allows to patient 85 (81,7%) to conserve extremity and to decrease metastasis in 2 times by comparison with pure surgical treatment.

Mirza A.Gafur-Akhunov, Khurshid G.Abdikarimov, Ulugbek F.Islamov, Djamila Sh.Polatova, Sundr D.Urunbaev, Fakhriddin E.Nasritdinov

National Oncology Research Centre, Tashkent, Uzbekistan

**Aim:** analysis of endoprosthetics results of knee joint in the treatment of tubular bone tumor.

**Materials and methods:** Endoprosthetics of knee joint have been performed in 96 patients, on the occasion of tumor of distal part of thigh (70) and proximal part of shin bone. Men were 62, women-34. Average-24, 7. Length of damage by bones was composed from 6 till 20 sm. By morphological structure, in 44 patients has been detected osteosarcoma, in 15 – chondrosarcoma, in 1 – paraostal sarcoma, in 36 – giant cellular tumor. To the course of no adjuvant and adjuvant chemotherapy have been performed in osteogenic and low differentiated form of chondrosarcoma. The resection length of bones composed from 10 till 24 sm. In the tumor of proximal part of shin bone was used muscular plastics from medial legs of sural muscles.

**Results:** Complications appeared in 22 patients (22,9%) – infections of prosthetics area (10), instability endoprosthetics (12), in the third cases these complications have been combined. In 4 cases (40%) infectious complications have been stopped conservatively. Operative intervention in different volume was made in 6 cases: 4 – crippling operations, 1 - reendoptosthetics, 1 – removal of endoprosthetics with imposition of compression-destruction osteo synthesis apparatus. The cause of instability in 4 (33,3%) cases was loosening legs of endo prosthetics in marrowy channels, in 7 (58,3%) – disorders of construction (fracture of leg-5, fracture of articulate part-2) in 1 (8,4%) – reduction of construction (screw of articulate part). Crippling operations have been performed in 3 patients with loosening of endoprosthetics legs in combination with contamination and in 2 with leg fractures of endoprosthetics. Reendoprosthetics was performed in 4 cases, in 1 – endoprosthetics reconstruction and at present knee joint has been fixed by external removable joint -immobilizer in 2 patients with fracture of articulated part. Functional condition of knee joint by scale MSTs 76% after resection of proximal part of shin bone and 91% after resection of distal part of thigh bone.

**Conclusion:** Endoprosthetics is a standard of surgical treatment in bone tumors constituent of knee joints, which allows to get satisfactory functional results and improves the quality of patients life.

## LIMB PRESERVATION SURGERY IN THE LOCALLY ADVANCED SOFT TISSUE SARCOMA OF THE ELBOW JOINT REGION.

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Matsumoto S., Shimoji T., Ae K., Tanizawa T., Gokita T.,

Department of Orthopedic Oncology, Cancer Institute Hospital, Tokyo, Japan

**Introduction:** The elbow joint region has structurally important functions such as median, radial and ulnar nerves, and brachial vessels. This explains that after removal of locally advanced tumor around the region, reconstructions of joint function, major skin defect and nerve function are prerequisite. We have successfully treated subjects of severely advanced sarcoma around the region.

**Methods:** Extracapsular resection for the elbow joint was performed in all cases. Neurovascular bundles were made *In Situ* Preparation (ISP). In the reconstruction treatments, an elbow joint was replaced by an artificial joint, Coonrad-Morrey, and recycled bone. In the upper arm skin defect treatment, functional LD flap for the Triceps and shortening of humerus in 2-3 cm were introduced, while for the forearm skin, free anterolateral thigh was performed. And for the functional defects of radial nerve, tendon transfer was adequately performed.

**Cases:** From 2008 to 2009, four (4) subjects with STS around elbow joint were performed without making a preoperative treatment. Pathological diagnoses performed were two (2) cases of synovial sarcoma; one in MFH and another in Extrasketal OS.

**Results:** The surgical margin in all cases was adequately maintained. There was no local recurrence created. Prognoses were three (3) cases in CDF and one (1) case in AWD. Concerning the functional outcome attained was 79 to 90 degrees in active ROM, and 22-26 points in ISOLS. Complications confirmed were temporary nerve palsy in two (2) cases and one case of infection.

**Conclusions:** Combination treatments with the state-of-the-art techniques including artificial joint, recycled bone, skin flap, shortening of humerus and ISP contributing to the limb preservation surgery in locally advanced sarcoma around elbow joint region were successfully made.

**Reference:** Matsumoto S. et al.: "*In situ* preparation": new surgical procedure indicated for soft-tissue sarcoma of a lower limb in close proximity to major neurovascular structures. *Int J Clin* (2002)7:51-56

Albertini Ugo<sup>1</sup>, Boffano Michele<sup>1</sup>, Boux Elena<sup>1</sup>, Marone Stefano<sup>1</sup>, Linari Alessandra<sup>2</sup>, Gino Gian Carlo<sup>1</sup>, Brach del Prever Elena<sup>1</sup>, Piana Raimondo<sup>1</sup>

1 Oncologic and Reconstructive Orthopaedics – AO CTO/Maria Adelaide Torino, Italy

2 Pathology Department – AO OIRM/Sant'Anna Torino, Italy

**Objectives:** Allograft is one of the options in the reconstruction of the extensor mechanism after bone and soft tissue sarcoma resection, quadriceps or patellar tendon rupture after total knee replacement and knee replacement revision surgery. The aim of the study is to understand the healing process at the junction allograft-patellar tendon through a microscopic study.

**Materials and Methods:** Woman, 61 years old, malignant fibrous histiocytoma of the distal femur with intra-articular involvement underwent an extra-articular resection with wide margins after preoperative chemotherapy. The distal femur was replaced with a modular megaprosthesis (Megasystem C, Link Italia, Milano) and the extensor mechanism was reconstructed with an allograft. The allograft was supplied by the local Musculoskeletal Tissue Bank. The suture was performed by Flexidene no.2 (Braun, Germany). Functional results: active flexion (80°) and active complete extension, walking unaided without any pain after 4 months from surgery and stable till 9 months. Unfortunately after 9 months the patient had a massive local recurrence and underwent a hip disarticulation. At the macroscopic examination of the limb the integration between allograft and patellar tendon was complete and the junction was sampled and sent for histopathologic examination. Histologic examination was performed with a light microscope (H&E stain).

**Results:** Histological analysis showed changes indicative of chronic inflammation, fibrosis and foreign body reaction in correspondence of the autologous tendon. These changes were observed to progressively modify towards the allograft, presenting degenerative changes without abrupt discontinuity.

**Conclusions:** The examined specimen shows that, although degenerative changes are present, there is a good functional result. This is an important result which helps in the comprehension of the healing process of allograft and the integration with autologous tissues. To our knowledge no other studies investigated the *in vivo* structure of the junction allograft-tendon after 9 months from surgery. Further studies are mandatory to comprehend and improve the healing process. In particular they should be focused on long term changes and on the unpredictable evolution of a chronic inflammation process.



Duarte R. ; Vieira Ferreira N.; Frada T.; Maia R.; Fidalgo R.; Igreja C.; Vieira da Silva M.; (Braga, Portugal)

**Introduction:** Giant cell tumors (GCT) of bone are benign tumors that occur predominantly around the metaphyseal area of long bones. The treatment remains controversial because of their high recurrence rate. The majority are treated by aggressive curettage or resection followed by methacrylate cement reconstruction.

**Material and methods:** A 40 year-old woman was admitted in our institution in January 1995 with a pathologic supra and intercondylar fracture of the right femur. Radiographically she presented a lucent lesion located eccentrically in the internal femoral condyle. She was submitted to open reduction, intralesional curettage followed by methacrylation and fixation with cancellous bone screw. The histological findings confirmed the suspected diagnosis of a giant cell tumor – Campanacci grade one.

During the follow-up period there were no signs of local recurrence or radiolucent zone at the bone-cement interface.

Fifteen years after the surgery, the patient started to present several gait limitations and knee pain. Radiological examination demonstrated an extensive osteoarthritis (Kellgren-Lawrence 4). The MSTS score was 3/30.

The patient was elected for total knee replacement (TKR). Intra-operatively the cemented area looked stable and the surgeons decided to remove the cancellous bone screw and to perform a primary TKR without removing the cement.

**Results:** One year after TKR the patient was satisfied with the clinical and functional outcomes. The range of motion of the right knee was 0 degrees extension and 110 degrees flexion, and the patient was able to walk without pain and gait supports. VAS score was 1 and the MSTS score changed from 3/30 preoperatively to 26/30. No radiologic signs of failure in bone-cement interface were detected.

**Discussion:** Osteoarthritis of the knee joint occurred 15 years postoperatively after treatment of a GCT with an intraarticular fracture at presentation. Reconstruction of a knee that was damaged by cement used in the treatment of a giant-cell tumor is sometimes difficult. There are several surgical options, such as cement removal and filling with autologous bone graft followed by TKR; en-bloc resection of the distal femur and reconstruction with a modular oncology femoral and knee prosthesis; and knee arthrodesis. Our option, primary TKR without cement removal, as minimally aggressive solution, becomes till now an excellent option.

**Conclusions:** Giant cell tumors with an associated intra-articular fracture remain a challenging problem to treat at presentation. Current solutions to this pathology evolve in high percentage to osteoarthritic changes upon several years post-op, which then, arouses as another surgical demanding problem.

The option to maintain the cement becomes effective, safe and allows the use of a primary prosthesis that provides immediate mobility and stability.

Delépine G<sup>1</sup>, Delépine F<sup>2</sup>, Cornille H.<sup>1</sup> Delepine N

<sup>1</sup>Oncologic unit Raymond Poincaré Hospital Garches France

<sup>2</sup>Clinique du parc impérial 28boulevard du tzarevitch 06045 Nice France

**Objectives:** With effective chemotherapy the gold standard for limb salvage is wide resection. Consecutively primary total femur resection is nowadays rarely indicated. Nevertheless with long follow up some secondary indication appeared and justify this review of our cases.

**Materials:** Between 1981 and 2011 we performed 276 femoral resection for bone sarcoma among them 14 patients had total femur resection. Median age of patient is 14.5 (79-4.9) Histology of tumour are osteosarcoma in 8, Ewing's in 4 (2 initially metastatic) and dedifferentiated chondrosarcoma in 2.

The indication for total femur resection were : very huge tumour in 3, inappropriate previous surgery with femoral nailing in 3, persistent infection of an upper massive prosthesis in 1, local recurrence in 1, and mechanical failure in 6.

The first patient was reconstructed with a monobloc custom made prosthesis; the other benefitted of composite implant including hip and knee prostheses, cement and sometimes growing component or allograft.

**Results:** 4 patients died of disease after 6 to 18 months The 10 other are disease free survivors with a median follow up of 15 years. 8/10 survivors have a still their limb and their prostheses.

Complications included severe ischemia in 1 (monobloc prosthesis was 3 centimeters too long) and, hip dislocation in 2.

Deep infection, secondary or late appeared in 6 patients (50% of cases!), due to the bad coverage of the prosthesis or reoperation for lengthening. Deep infection is the most frequent and most severe complication. It was the reason for secondary amputation in 2.

Stiffness of the knee (Average flexion 45°), leg discrepancy and frequent necessity of crushes for long walking (4/8) explain that the functional result of the 8 patients with prostheses is never excellent, but only good (5) or fair (3).

**Conclusions:** Total femur reconstruction give much better function than amputation even if knee stiffness is usual. Composite reconstruction is more flexible than custom made monobloc prosthesis and no loosening between the 2 implants appeared even with very long follow up.

The adjunction of high dose Vancomycine in cement decreases the infectious risk and seems the best preventive measure of the most severe complication of this salvage procedure.

## MODULAR PROXIMAL FEMORAL REPLACEMENT IN METASTATIC BREAST CANCER

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GL Cribb, P Cool, DH Williams

Robert Jones and Agnes Hunt Orthopaedic Hospital - Oswestry - UK

**Objectives:** Breast cancer is the most common cancer in the UK and over half of patients who develop metastatic disease will have bone metastases

Proximal femoral replacement is often the treatment of choice for impending or actual fractures of the proximal femur in metastatic breast disease as fixation devices often fail. It however is a costly procedure, which is poorly remunerated.

We were keen to establish the outcome of this procedure at our institution for metastatic breast disease.

**Materials and Methods:** Data was collected from our tumour database of all patients who had undergone proximal femoral replacement since 2004 with at least 6 months follow up.

**Results:** We identified 34 procedures, which had been performed in 32 patients (2 have bilateral implants). Seventeen procedures were performed for fracture, 15 for impending fractures and 2 for revision of failed internal fixation devices. The average age of the patients at time of procedure was 59.92 (range 29-83). The procedure was performed on average 5.26 years (0.03-20.87) after cancer diagnosis.

All procedures used the Modular Stanmore Mets Proximal Femoral Replacement. No patients had an acetabular procedure.

Average inpatient stay post procedure was 13 days (range 6-29)

There was one inpatient complication of a chest infection. A further patient developed deep sepsis seven months post surgery, she has several wash out procedures and remains well with a draining sinus. There have been no dislocations.

There are 9 patients (10 implants) who are still alive. The average time to death post procedure was at an average of 14.01 months (1.05-63.45). There were no deaths during the inpatient stay for the procedure at our institution.

The average TESS score of the surviving patients is 48 (37-60) at 6 months post surgery.

**Conclusion:** In conclusion proximal femoral replacement is a safe procedure with a low complication rate.

Vasileios Kontogeorgakos<sup>1</sup>, George Kyrgias<sup>2</sup>, Sokratis Varitimidis<sup>1</sup>, Konstantinos Malizos<sup>1</sup>

1. Department of Orthopaedic Surgery, University of Thessalia, Larissa, Greece
2. Department of Radiation Therapy, University of Thessalia, Larissa, Greece

**Introduction:** Loss of the thumb results in almost 50% of the hand function. This can be the result of either congenital thumb anomalies or traumatic or oncologic amputation. Tumors of the thumb constitute a unique group as multidisciplinary approach is important for diagnosis and functional treatment. Here we report on a patient who presented with a 1st ray resection because of diffuse squamous cell carcinoma and bulky tumor recurrence.

**Material and Method:** A 47 years old man was treated for chronic skin infection of the thumb with repeated wound dressings and per-os antibiotics for 6 months. The skin lesion and erythema was evolving and the patient underwent 1st ray resection. Pathology report revealed a squamous cell carcinoma, with negative resection margins. No further treatment was offered at that time. The tumor locally recurred and the patient referred to us 4 months after index operation, for further evaluation and treatment. At presentation the patient had a bulky tumor recurrence without nodal involvement. A 3cm wide resection of the recurred tumor was performed followed by 45 Gy radiation therapy. Twenty days later an index pollicization was performed with a free radial forearm flap for web reconstruction.

**Results:** The 2nd post-op day, the patient was able to flex the pollicis-index finger and bring the terminal phalanx in opposition to the middle finger. At one month, he was able to grasp and hold light items. Satisfactory function in daily activities was achieved. However, 6 months after presentation to us, the patient developed axillary node metastatic disease rapidly evolving. The patient died 2 months later.

**Conclusion:** Squamous cell carcinoma is well known for 2 characteristics: may present as infection and gives metastases to regional nodes. However initial biopsy and accurate pre-op diagnosis is important for staged treatment. Oncologic thumb amputations are rare. Resection of the thenar muscles decreases the maximum functional result that can be achieved. However, even with extensive tissue loss, combined reconstructive procedures of index pollicization and soft tissue flap for web reconstruction can significantly improve hand function.

AE Wijsbek, BL Vazquez-Garcia, R Grimer, S Carter, R Tillman, A Abudu, L Jeys.

Royal Orthopaedic Hospital – Birmingham (UK)

**Introduction:** Giant cell tumour (GCT) of the proximal femur (PF) represents only 5.5% of all GCTs. Many will present with a pathological fracture and most will already have significant bone destruction by the time of diagnosis. Although conservative treatment with curettage (+/- bone graft) is usually used for most GCTs, we questioned whether this was ever successful in GCT PF.

**Methods:** Retrospective review of all patients treated for primary GCT PF. Case notes and imaging studies were reviewed to identify the success of treatment in terms of hip preservation and tumour control.

**Results:** 24 patients had GCT PF over a 28-year period. 15 were male and 9 female and the mean age was 31.5 (range 17-74). 11 had a pathological fracture at time of diagnosis; all were treated with either EPR or THR. Treatment was with a THR in 9, EPR in 5 and curettage in 10. Local recurrence arose in 5 patients (21%), all within 3 years. LR arose in 2 treated by THR (22%), 0 by EPR and 3 by curettage (30%). Further surgery for any cause was required in 8 and was due to LR in 5 and mechanical failure in 3. Of the 10 patients treated initially with curettage, 3 had a THR for LR and 1 EPR for mechanical failure. Thus, eventually, 18 patients ended with an arthroplasty and only 6 (25%) kept their own hip joint.

**Conclusion:** GCT PF is fortunately rare. In our hands, patients without a pathological fracture treated with curettage (+/- bone graft) had in 60% a successful outcome – but there is a 30% rate of LR in this group and a 10% risk the construct will fail. In the presence of a pathological fracture, or older patient, arthroplasty is a safer option.

# RECONSTRUCTION AFTER RESECTION OF PRIMARY OR SECONDARY TUMOURS IN PROXIMAL FEMORAL BONE: COMPARISON OF DIFFERENT TYPES OF DEVICES

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M. Maechler<sup>1</sup>, J. Friesenbichler<sup>1</sup>, P. Sadoghi<sup>1</sup>, W. Maurer-Ertl<sup>1</sup>, A. Leithner<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Medical University of Graz, Auenbruggerplatz 5, A-8036 Graz, Austria

**Introduction:** Life expectancy of patients with malignant soft tissue and bone tumours or metastases has taken great improvement within the last decades due to the progress of modern chemotherapy regimes. Investigations proved that a limb-sparing therapy is possible in about 90% in case of malignant bone or soft tissue tumors in the upper and lower extremity is necessary. Therefore the question arises, which reconstructive procedure allows the best outcome. The aim of this study was to evaluate the prosthesis' survival rate and complications in patients with surgical reconstruction after treatment of proximal femoral tumors.

**Material And Methods:** Between April 1996 and September 2011, 198 patients underwent surgical reconstruction after surgical treatment of primary bone tumours or metastases (55 primary tumours; 143 metastases). These cases were reviewed retrospectively. Complications were analyzed according to the classification of Goslings and Gouma and Henderson et al. The prosthesis' survival rate was calculated according to Kaplan-Meier.

**Results:** In 73 cases (group 1; f:m = 40:33 males (mean age: 56 years) a modular proximal femoral tumour prosthesis was implanted. There were 39 patients with primary bone tumours and 34 cases of metastases. In 110 cases (group 2; f:m = 67:43 males (mean age: 66 years) a hemiarthroplasty was performed. This group included three patients with primary bone tumours and 107 patients with metastases. Fifteen patients (group 3) with nine females and six males (mean age: 55 years) were treated with total hip arthroplasty (7 primary tumours and 8 metastases). There were 25 complications needing revision surgery (13 infections, five cases of structural failures, four cases of soft tissue failures and three cases of aseptic loosening). Proximal femoral reconstruction devices had a survival rate of 77% after 12 months and 65% after 60 months. Calculated implant survival for hemiarthroplasties was 97% after 12 months and 91% after 60 months, whilst total hip arthroplasties had a survival rate of 83% and 71% for the same period. In total, prosthesis' survival rate was 86% after 12 months and 75% after 60 months. The difference between implant survival for several types of devices was statistically significant ( $p=0,016$ ).

**Conclusion:** Surgical reconstruction after resection of proximal femoral bone tumours or metastases revealed adequate survival rates, independently from type of prosthesis, which was used for reconstruction. However, longer follow-up is needed in order to address the mid-term and long-term survival rates.

## TREATMENT OF BONE DEFECTS CAUSED BY THE CURETTAGE OF BENIGN TUMORS WITH UNSTABLE OSTEOSYNTHESIS WITHOUT GRAFTING

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*Edgard Eduard Engel, Leandro Rodrigues Brandi, Pedro Mendonça Cyranka, Nelson Fabrício Gava*

*Faculty of Medicine of Ribeirão Preto University of São Paulo, Ribeirão Preto, Brazil*

Despite its popularity, the need to fill bone defects after benign lesions curettage is not well established in the literature. Autogenous and allogeneic grafts, bone substitutes, and bone cementing are utilized for this purpose and have advantages and disadvantages. The risk of relapse or fracture, and the capacity for bone remodeling are the parameters that guide the surgeon's choice.

Thirteen patients with a mean follow-up time of 19 months (6-48 months) underwent curettage and unstable fixation without grafting of benign tumors. Similar to bridge plate osteosynthesis, rigid internal fixation permits a certain movement in the weakened region permitting bone remodeling according to Wolf's law. Radiographs immediately, one month, and six months after surgery were analyzed and bone remodeling area was measured.

For patients with lower limbs lesions full weight bearing was allowed 3.5 weeks (0 to 12) after surgery. No patient presented fractures or complications related to the early weight bearing. Radiograph measurements showed a reduction of 20% of the bone defect after the first month and of 56% after sixth months.

These preliminary results suggest that the unstable fixation protects patients submitted to curettage from fractures, but does not interfere with bone remodeling, allowing the natural filling of the lesion.



In the treatment of bone tumors margins are very important. The first goal is always to obtain an adequate margin. Resection of for example bone tumors results in defects that require reconstruction, the larger the defect, the more difficult the reconstruction and generally speaking the poorer the function. The reconstruction and post op period are often difficult due to allograft formation difficulties and complications as long in growth time, infections and fractures.

The use of computer assisted surgery (CAS) navigation systems can be an elegant alternative to the standard approach of fluoroscopy assisted resection and unassisted reconstruction. CAS has already been described as able to reliably plan resection planes creating adequate margins in bone tumor operations; furthermore it can be used to perform the reconstruction with pre-planned resection planes. As an example, CAS resection and reconstruction can be applied to hemicortical resections.

Some low grade bone tumors can be resected close to the tumor leaving a partial defect in the host bone instead of a segmental defect. The reconstruction can be done with a so-called inlay graft. In low grade malignant tumors margins can be smaller, resulting in less tissue damage, smaller defects and better functional outcome. Hemi-cortical resections leave the cortex partially intact as a natural splint. This surgical technique for the treatment of low grade malignant bone tumors was first described in 1982 by Campannaci et al. Hemicortical resection is considered a safe alternative to a larger segmental resection for low malignant bone tumors. However the operation is technically demanding and complications as fractures are reported. [2]

First a fresh frozen donor bone has to be found in the bone bank with, optimally, comparable dimensions to the host bone. A CT-scan of the same configuration (i.e. slice thickness) was performed from both the host and the allograft. These scans are imported in the CAS system and matched by hand to find the optimum overlay in order to find the best fitting part to take the inlay graft from. The planned resection planes from the setup of the host bone are then copied to the setup of the allograft.

Normal CAS setup is performed with a tracker attached to the bone after exposure of the bone. Matching is done with reference points- and surface-matching, till an accurate match is reported. The pointer tool is then used to identify and mark the edges and entry points of the planned trapezoid shape. The excision planes are marked with a pen and checked with the pointer tool for accuracy. An oscillating bone saw is used to perform the preplanned trapezoid shaped resection. The resection planes were checked again after resection for accuracy. The exact same procedure can then be performed on the allograft bone.

The means of using CAS in the reconstruction after tumor resection is relatively new in orthopedics; in craniomaxillofacial surgery it is becoming more common. Last year we reported on one case of CAS resection and reconstruction in an adamantinoma, in a 17 year old boy. The result was good, with rapid in-growth of the allograft. Currently we have operated four patients with benign bone tumors, all with good follow-up and no complications, using the computer assisted hemicortical resection and allograft reconstruction approach. CT controls are currently being performed as to quantify the accuracy of allograft reconstruction by measuring the gap between host bone and allograft after surgery. Results are not available as the scans are still being analyzed. In our eyes the CAS approach to these, albeit rare conditions, is an improvement over the current approach. It proves that CAS can be used in all kinds' of bone reconstructive surgery. The time required for the surgery is greatly reduced, and the difficulty is decreased. We hypothesize that the increased accuracy in navigation decreases the gap between the allograft and the host bone, promoting faster in growth, shorter recovery time and possibly lower fracture rates.

Alternatives for assisted reconstruction could be pre-planned saw blocks designed for both the patient bone and the allograft bone. Navigation in this setting would in our eyes still be required in attaining an accurate placement of the saw block. As the blocks are custom made this can be quite expensive. Another alternative is the pre fabrication by rapid prototyping or other means of a filler material. Accurate resection has to be performed for the filler to fit, navigation is again required.

As the navigation now offers accurate guidance, the biggest factor of deviance is the means of resection. As the oscillating saw, as far as we now, cannot be accurately tracked by the CAS system, an alternative means of resection would be ideal in these types of operations. Adjustable saw blocks that are placed with the CAS system can be a possibility. A fully automatic navigated means of resection would have the preference.

#### **Referenties:**

[1] Deijkers RL, Bloem RM, Hogendoorn PC, et al.: Hemicortical allograft reconstruction after resection of low-grade malignant bone tumours. J Bone Joint Surg Br 2002;84:1009-1014.

# SAFETY OF VACUUM ASSISTED CLOSURE THERAPY FOR INFECTIONS AND WOUND PROBLEMS AFTER WIDE RESECTION OF SARCOMAS

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M. Ayvaz, K. Buyukdogan, M. Tokgozoglu (Ankara, Turkey)

**OBJECTIVE:** One of the most challenging complications of tumor surgery is covering of implant with healthy soft tissue and prevention of infection. Generally a skin necrosis around the wound occurs in these patients after surgery and this causes a great problem with co-applied chemotherapy. Patients with such problems who are applied Vacuum Assisted Closure (VAC) are assessed in this study.

**METHOD:** 13 patients treated with VAC for wound problems after tumor resection between 2006-2009 were evaluated retrospectively. Mean age of patients (10 male, 3 female) was 37 (15-74). Pathologic diagnosis were giant cell tumor in 3 patients (2 pelvis, 1 distal femur), chondrosarcoma in 3 patients (2 pelvis, 1 proximal tibia), osteosarcoma in 4 patients (proximal tibia), liposarcoma in 2 patients (1 thigh, 1 gluteal) and malign mesenchymal tumor in proximal femur. Sponge used in VAC therapy was changed every 72 hours and every time cultures revealed from wound base and patients were followed by weekly infection parameters (ESR, CRP). IV antibiotic therapy was administered according to culture results. When the culture results were negative and serological markers were normalized, permanent soft tissue reconstruction was performed.

**RESULTS:** Mean follow-up time of patients after wound place reconstruction was 21-3 months (14-38). In only one patient VAC was re-applied due to recurrent local infection. In the final assessment of the patients no tumor recurrence or distant metastases were found. There were no prosthesis infection. No complications due to VAC therapy were seen.

**CONCLUSIONS:** VAC therapy is safe and effective for treatment of wound problems and infections after wide resection of sarcomas.

# RECONSTRUCTION OF THE PROXIMAL HUMERUS AFTER WIDE RESECTION OF CAMPANACCI'S GRADE III GIANT CELL TUMOR: CASE REPORT

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Luís Dias da Costa; Vânia Oliveira; Daniel Soares; Luciana Leite; Pedro Leite; Pedro Cardoso.

Centro Hospitalar do Porto, Hospital Santo António – Oporto - Portugal

**Introduction:** Giant cell tumor (GCT) is a benign but often locally aggressive neoplasm and is known for its unpredictable behavior, characterized occasionally even by metastases.

GCTs of the proximal humerus make up a minority of reports cases, and their treatment is guided by Campanacci's system and Enneking staging.

The gold standart treatment for GCT is the curettage and cementation of the cavities, however when we talk about Campanacci's grade III, the choice of a conservative treatment or a wide resection is controversy, but the most important issues of limb-salvage surgery of proximal humerus are to maximize local control of the tumor, to preserve both elbow and hand functions and to improve shoulder function and stability.

Authors present a case report of a patient with an extensive GCT of the proximal third of the humerus treated by a wide resection and reconstruction with a reverse total shoulder arthroplasty, with a very good outcome functional result.

**Case Report:** A 53-year-old male with clinical history of severe pain and swelling in the right shoulder over a period of 3 months, associated to marked shoulder function incapacity.

The radiographs showed a pathological fracture in the proximal third of the humerus through a huge osteolytic lesion.

The computed tomography scans were suggestive of an aggressive lesion.

The trucut biopsy confirmed a GCT.

Wide resection of the proximal humerus was performed and the articulation was reconstructed with a reverse total shoulder arthroplasty.

In the early follow-up (3 weeks), a dislocation of the prosthesis occurred and an open reductions was needed.

No other dislocation or complication was reported till the last follow-up (3 years).

No local recurrence was observed.

The patient keeps without pain and with an excellent shoulder function, after physiotherapy

The score of Constant was 76 in the last follow-up.

**Discussion/Conclusion:** The main treatment to Campanacci's grade III stills controversial. Some authors defends the curettage and bone grafting or cement because the poor functional results of the wide resection.

However, we believe that when lesions involve obliteration of the cortical bone and extension into the soft tissue, wide resection should be performed, especially if a pathologic fracture is present, to prevent recurrence.

In our case report, despise the dislocation of the prosthesis in the early follow-up, the patient presents an excellent range of motion, probably better than if a conservative procedure had been done.

# BONE SARCOMA OF THE LOWER ARM/ WRIST. RECONSTRUCTION WITH NON-VASCULARISED FIBULAR GRAFT IN CHILDREN: REPORT OF 2 CASES

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Fredrik Vult von Steyern<sup>1</sup> MD PhD and Antonio Abramo<sup>2</sup> MD PhD

Departments of Orthopedics<sup>1</sup> and Hand Surgery<sup>2</sup>, Skåne University Hospital, Lund, Sweden

**Objective:** Autologous vascular fibular grafts are useful for reconstruction of skeletal defects in tumour surgery. However, there are reports showing that results from non-vascularised grafts are comparable to vascularised (Krieg and Hefti, 2007). Grafts heal at a similar rate, and biological activity, assessed as hypertrophy of the graft and callus formation when fractures occur, has been observed irrespective of method. Moreover, there are also considerable advantages with non-vascularised grafts, eg less complicated surgery, shorter operation time and less morbidity at the donor site. Still, some locations with limited amount of surrounding soft tissue/muscle mass, eg the lower arm/wrist, have been suggested to be less suitable for non-vascularised grafts. This may however not be true. A series of cases with distal radius tumours reconstructed with non-vascularised proximal fibular grafts after excision was published in 2004 (Maruthainar et al.). This study presented good functional outcome for the patients, but included only adult patients and the majority were not treated with chemotherapy.

We here report preliminary but promising results from 2 cases where non-vascularised fibular grafts were used to reconstruct skeletal defects after surgery of bone sarcomas in the lower arm/wrist in children.

## Patients and Methods:

Case 1; Girl, 10 y, with osteosarcoma of the left distal radius. Localized disease. Chemotherapy was given, pre- and postoperatively, according to the EURAMOS-1 protocol. Surgery was performed with excision of 11 cm of the distal radius. Histopathologic examination showed free surgical margins and good chemotherapy response. A non-vascularised proximal fibular graft, including the fibular head, from the ipsilateral side was used for reconstruction. The graft was fixed to the proximal radius with a plate and a flap from the ECRB was used to adapt the distal radius/ulna. The wrist was fixed with pins for 3 weeks. The graft was made longer than the excised radius to compensate for expected growth of the ulna.

Case 2: Girl, 13 y, with Ewings sarcoma of the right distal ulna. Localized disease. Chemotherapy, pre- and postoperatively, was given according the Euro Ewing-99 protocol. Surgery was performed with excision of the distal ulna, osteotomy 11 cm proximal to the distal physis and through the physis, the epiphysis and TFCC-lig were spared. Histopathologic examination showed free surgical margins and good chemotherapy response. Reconstruction was made using a diaphyseal non-vascularised fibular graft from the ipsilateral side. The graft was fixed with a plate proximally and with an ulnar pin-plate distally.

Both girls are followed according to protocols, but in addition scintigraphy of the lower arms was performed 1 year postoperatively. FU this far is 26 (case 1) and 16 (case 2) months with no evidence of disease.

**Results:** The grafts healed radiographically with the anastomoses no longer visible after 11 and 9 months, respectively. In addition, scintigraphy 1 year after surgery revealed revascularisation of the grafts. In case 2 there is partial regeneration of the fibula at the donor site.

In case 1 the epiphysis of the graft slipped 4 months after surgery. This was treated with cast for 6 weeks. There is now subluxation of the carpus, but no pain. She has limited range of motion of the wrist (active flexion/extension 15 degrees and pro-/supination of about 45 degrees). Sensibility and motion of the fingers are normal. The left, operated, hand/wrist was and is still, after surgery, her dominant hand. The ulna has grown and there is no longer any exterior sign of ulnar deviation of the wrist. At the donor site she has occasionally light discomfort when running, but no pain. The ankle is stable.

In case 2 no complications occurred during healing of the graft. The wrist is stable and she has full range of motion. Radiographically there is partial regeneration of the fibula at the donor site. She has occasional discomfort from the lower limb when running, but no pain and the ankle is stable.

**Conclusion:** We here report preliminary good clinical and radiological results using autologous non-vascularised fibular grafts for reconstruction of skeletal defects of the lower arm/wrist in 2 children. The grafts healed although in the case with proximal fibular graft the epiphysis slipped, resulting in a subluxation of the carpus. Maybe this event could have been avoided by internal fixation of the epiphysis.

BL Vazquez-Garcia, AE Wijsbek, R Grimer, S Carter, R Tillman, A Abudu, L Jeys.

Royal Orthopaedic Hospital – Birmingham (UK)

**Introduction:** Limb salvage in the upper limb is usually fairly straightforward but in certain situations conventional methods of limb salvage (amputation or endoprosthesis) are not possible or lead to poor outcomes. We describe 14 cases where irradiation and reimplantation of bone has been used to solve a difficult challenge.

**Methods:** Retrospective review of all patients treated in our institution with irradiation and reimplantation of the upper limb. We assessed the case notes and imaging studies to determine the success of this technique.

**Results:** 14 patients were treated with irradiation and reimplantation of the bone graft in the past 15 years. Mean age was 24 years (5-65 years), 9 female and 5 male. The bone tumours were Ewing sarcoma (4), osteosarcoma (6), osteochondroma (1), chondrosarcoma (2) and epithelioid haemangioendothelioma (1). They were situated in the humerus (9) (middle 3, distal 4, proximal 1, total 1), total scapula (3), ulna (1) and metacarpal (1). The mean follow-up time was 51 months (1-124). 4 patients (29%) had a non-union following the reimplantation, all were treated with bone graft, 2 preceded with fracture. 2 (14%) had a fracture following the reimplantation. In three very young children the technique was used as a staged technique to replace the total humerus, all three having an endoprosthesis when they were older. Two patients died of metastases but there were no local recurrences. Superficial infection arose in one patient, ulnar nerve paralysis in one.

**Conclusion:** Irradiation and reimplantation of bone is a useful method of biologic reconstruction of upper limb tumours in selected patients. It should be considered when alternatives are not readily available or likely to have a worse outcome.

# RESULTS OF 19 REVERSE ALLOGRAFT-PROSTHESIS COMPOSITE RECONSTRUCTIONS OF THE PROXIMAL PART OF THE HUMERUS AFTER ONCOLOGIC RESECTION

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Even J<sup>1</sup>, Bartoli MS<sup>2</sup>, Anract P<sup>1</sup>

<sup>1</sup>Pole osteo-articulaire Chirurgie Orthopedique, Oncologique et Traumatologique B, Hopital Cochin, Paris, France <sup>2</sup>Scuola di Specializzazione in Ortopedia e Traumatologia, Università Statale di Milano, Italia

**INTRODUCTION:** Proximal humerus is the 3<sup>rd</sup> most common site for bone malignancies. Wide resection of the affected bone segment with the surrounding soft tissues is mandatory in order to achieve adequate margins. Options for reconstruction include allograft arthroplasty, endoprosthetic arthroplasty, allograft-composite prosthesis, clavicle pro humero and arthrodesis. Use of allograft-composite prosthesis is a solution which theoretically combines both benefits of osteoarticular allograft and megaprosthesis. Compared with osteoarticular allograft, it avoids subchondral fracture; compared with megaprosthesis it allows soft tissue tendinous and capsular attachment and restoration of bone stock. We present our experience with reverse prosthesis combined with proximal humeral allograft.

**MATERIALS AND METHODS:** We retrospectively reviewed patients treated in our institution for primitive tumours of the proximal part of the humerus who underwent reconstruction with allograft reverse shoulder prosthesis after resection type I according to the Malawer classification or S345 according to the Musculoskeletal Tumor Society classification. We revised their clinical history, assessment, oncological treatment, surgical technique and follow-up. Clinical and radiographic outcome were evaluated.

## RESULTS:

### Population

Between 2001 and 2010, we treated 19 patients with tumors of the proximal humerus preserving the deltoid (mean follow-up 40 months). Histological diagnosis was 9 chondrosarcomas, 2 Ewing sarcomas, 1 telangiectatic sarcoma, 1 osteoblastic sarcoma, 1 parosteal osteosarcoma, 1 synovial sarcoma, 2 giant cell tumours, 1 histiocytic fibroma. One patient had pulmonary lesions at diagnosis.

### Surgical procedure

Deltoid muscle was preserved in all patients except the anterior fibers of the muscle which were resected with the biopsy tract; deltoid distal insertion was detached and reinserted on the allograft. The anterior branch of the axillary nerve had to be sacrificed in 2 cases. Length of humeral resection ranged from 10 cm to 18 cm (Average: 14 cm). Reconstruction was achieved with total reverse shoulder prosthesis and fresh frozen allograft. Suture of the rotator cuff on the host allograft tendon was realized.

**COMPLICATIONS:** One surgical procedure was stopped because of bleeding during the resection of a giant cell tumour, reconstruction was done 24 hours later.

2 patients died of pulmonary metastasis, 2 local recurrences arose, one chondrosarcoma in a patient with Ollier's disease and one giant cell tumour.

8 patients had iterative surgery: 2 resections of local recurrence, 4 grafts for non union between the allograft and the humerus, 1 insertion of a lateralized spacer for iterative dislocation and 1 exploration and drainage for early infection.

### Clinical and radiographic outcome

Mean active abduction at last follow-up was 115° (range 40° to 180°; median 130°). On plain x-ray, evaluated with ISOLS radiologic score, we observed a significant allograft resorption in 50% of patients. This was not associated with loosening of the prosthetic stem.

**CONCLUSION:** Reverse composite prosthetic replacement is a reliable reconstruction technique for proximal humerus tumors. Its main advantages are the availability of tendon attachments to reconstruct the remnant host soft tissues, particularly the deltoid insertion, combined with the fixed fulcrum given by the reverse design. In our opinion, when it is possible to preserve a functional deltoid, this option is to be considered, in order to achieve a good long-term upper limb function.



Marco Manfrini, Marco Colangeli, Laura Campanacci, Nicola Fabbri e Pietro Ruggieri AUTHOR'S

Istituto Ortopedico Rizzoli, Bologna, Italy

**Introduction:** The use of expandable megaprotheses for knee reconstruction after distal femur resection in children affected by bone sarcoma has become more popular since the advent of custom-made devices that promised non-invasive lengthening procedure. The Repiphysis prosthesis was the first non-invasive expandable prosthesis available on the market. The lengthening is achievable through the energy stored in a compressed spring and released by an external electromagnetic field. The lengthening of the device is proposed in an outpatient basis.

**Objectives:** The authors reviewed the mid-term experience of a consecutive series of 15 children that received the Repiphysis at Istituto Ortopedico Rizzoli from 2002 to 2007.

**Method:** The clinical-radiographic evolution in a consecutive series of 15 children (9 males, 6 females; diagnosis: 14 HG Osteosarcoma, 1 Ewing Family Tumour), that had implanted a distal femur custom-made non invasive expandable prosthesis (Repiphysis WRIGHT), was analyzed.. Mean age at surgery was 8 years (range 6-11) and all patients received pre- and postoperative chemotherapy according to the diagnosis.

**Results:** At a 80 months (49-110), follow-up (f-up) 10 patients ) (67%) are alive with no evidence of disease (NED). One patient died under chemotherapy for drug toxicity. Two patients presented a LR and were retreated with an above-knee amputation at 6 and 19 months from the implant. Both died for diffuse disease at 11 at 28 months from the first surgery. Three other patients presented lung metastases during the follow-up. One patient is alive and NED, 60 months after the last toracotomy. The 2 others died at 20 and 28 months from the implant (one of these 2 children showed a postoperative infection and had the implant removed after 8 months). In summary 10 patients in complete remission underwent the lengthening program and are available for the evaluation.

The first 7 procedures (in 3 patients) were attempted in an outpatient basis with no anesthesia but they were unsatisfactory because of the difficulty to manage the young patients that reported sudden pain and burning sensation. Moreover it was clear that only a minimal lengthening was achievable without a complete muscle relaxation. All the successive 38 lengthening procedures (mean 4 for patient, range 1-5) were performed under anesthesia in a Day-hospital basis. The total lengthening of 381 mm was obtained but a great variability was observed with a range from 3 to 20 mm for procedure. Post-lengthening inflammation of the thigh with pain, stiffness and radiographic appearance of a radiolucent layer around the prosthetic body occurred in 6 cases after the third procedure. Eight patients presented radiographic and clinical signs of implant failure (metallic debris in the soft tissue, breakage of the spring, instability) and underwent a complete revision of the primary implant at a mean f-up of 61 months (range 51-82 months). Five males were still skeletally immature (age at revision 11-13) and were revised with other types of expandable megaprotheses while 3 females were revised with adult megaprotheses (age at revision 13-15) with a final limb length discrepancy from 0 to 3.5 cm.

**Conclusion:** In our hands Repiphysis prosthesis maintained only partially the offer of non invasiveness: general anesthesia was necessary to obtain the lengthening of the device and no control on the amount of lengthening was possible. Moreover the implant was too fragile and mechanically failed before the end of the expected complete lengthening determining the need of a second expandable prosthesis.



# IMPAIRED WOUND HEALING AFTER NEOADJUVANT RADIOTHERAPY AND RESECTION OF SOFT TISSUE SARCOMAS OF THE EXTREMITIES

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Y. Bakhshai<sup>1,\*</sup>, J. Rauch<sup>2</sup>, L. Lindner<sup>2</sup>, V. Jansson<sup>1</sup>, A. Baur-Melnyk<sup>2</sup>, H. R. Dürr<sup>1</sup>

<sup>1</sup>Orthopaedic Oncology, Dept. of Orthopaedic Surgery, <sup>2</sup>Ludwig-Maximilians-University Munich, München, Germany

**INTRODUCTION:** There is an ongoing question whether radiotherapy in soft tissue sarcoma should be applied pre- or postoperatively.

**OBJECTIVES:** Analysis of the influence of neoadjuvant radiotherapy on wound healing after tumor resection in patients with soft tissue sarcomas.

**METHODS:** 34 patients with soft tissue sarcomas had an intended wide resection. Preoperative radiotherapy was applied (mean 52 Gy), postoperative brachytherapy at a mean dose of 17 Gy. Impaired wound healing was analyzed prospectively. The mean follow-up period was 7 months.

**RESULTS:** 34 patients had either neoadjuvant radiotherapy (n=8) or radiotherapy and chemotherapy including local hyperthermia (n=26). R0 resection was achieved in 33 patients. Impaired wound healing occurred in 20 patients (59%). 17 patients had second surgeries (50%, 85% of patients with impaired wound healing). 4 of those 17 Patients had 2 or more interventions. 12 (71%) had had neoadjuvant chemo- and radiotherapy, 5 (29%) radiotherapy only. 4 (44%) of the 9 patients with tumors ≤ 5cm had second surgery. 13 (52%) of the 25 patients with tumors > 5cm needed further surgery. Regarding age Group 1 (age 23-45 y, n=11) showed 7 patients (64%) with revision surgeries, group 2 (age 46-67 y, n=11) 3 (27%) and group 3 (age >68 y, n=12) 7 (58%) revisions. 12 (35%) patients had an implantation of brachytherapy catheters following resection and underwent afterloading. 50% had wound healing disorders, all of them needed further surgery. With the combination of neoadjuvant chemo- and radiotherapy and adjuvant brachytherapy 5 (42% of the afterloading group) patients needed secondary surgery. Of those 5 patients one had to be amputated. Of the 2 patients that had received neoadjuvant radiation and adjuvant brachytherapy, without chemotherapy one had further surgery. 5 (15%) patients showed metastasis at the date of tumor resection. The mean follow up of those patients was 3,4 months. 3 had progressive multiple metastases on the latest report, one was in a stable and one in a regressive status. Of the 29 patients with no metastatic disease at time of surgery, 11 developed systemic tumor progression. We saw one patient (3%, resection status R0) with a local recurrence. He had neoadjuvant radio- and chemotherapy. At the time of the latest follow-up 3 patients had deceased. One patient died due to a septic complication following revision surgery, 2 patients died due to progressive disease.

**CONCLUSION:** Radiotherapy has proved to be effective in regard to local tumor control (3% local recurrence in this study). There are some reports, that local wound healing is mildly disturbed after neoadjuvant radiotherapy but on the long term the functional outcome seems to be better. Neoadjuvant chemotherapy alone does not seem to have an effect on wound healing after resection. In our series 59% of the patients developed wound healing problems, one patient died due to septic complications following revision surgery, one patient has to be amputated. 50% of all patients needed at least one revision. In patients treated by radiotherapy only 5/8 (63%) needed revisions, the combination of neoadjuvant chemotherapy and radiotherapy showed 12/26 (46%) revisions. The risk of wound healing disturbances is highly increased after neoadjuvant radiotherapy, more than reported in some of the sometimes enthusiastic literature reports.

**KEYWORDS:** radiation therapy, sarcoma, soft tissue, surgery, tumor, wound complication

Kasimatis G. (1), Errani C. (2), Bosco G. (2), Ruggieri P. (2). (1. Athens, Greece, 2. Bologna, Italy)

**BACKGROUND AND OBJECTIVES:** The aim of the present study was to review the long-term results in patients who had undergone modular prosthetic reconstruction of the knee, following a failed arthrodesis performed after the resection of bone tumors.

**METHODS:** We reviewed 16 desarthrodeses and prosthetic reconstructions of the knee following a failed artificial arthrodesis after bone tumor resection. Desarthrodeses and subsequent knee megaprosthesis were performed after breakage of the arthrodesis implant in 11 cases and following presumed eradication of infection in five cases.

**RESULTS:** The mean follow-up was 15.9 years. The mean post-operative range of knee flexion was 70°, but only four patients had active extension of the knee. Functional results, according to the MSTs system, were satisfactory in 11 patients. Complications included deep infections in five patients, aseptic loosening in three patients, breakage of the joint hinge in one patient, and patellar tendon avulsion in one patient. Despite a high rate of complications, all but two patients were satisfied.

**CONCLUSION:** Our findings indicate that conversion of oncological knee arthrodesis to total knee arthroplasty should be taken into consideration only after giving the patient extensive information about the high risk of serious complications.

## CUSTOM-MADE ANTIBIOTIC IMPREGNATED CEMENT MEGA-SPACERS FOR THE TREATMENT OF INFECTIONS IN MASSIVE BONE RESECTIONS

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M. Galli Serra, W. Parizza, C. Autorino (Buenos Aires, Argentina)

**Background:** Infection is a devastating complication following reconstruction with tumor endoprosthesis after massive bone resections. Two-stage reconstructive technique has been proved to be a safe and effective method in the treatment of this complex situation. One of the major concerns is that between stages patients may be uncomfortable with limited mobility and activity because of the magnitude of resection for tumor and infection control. The aim of the present study was to review a series of patients with massive bone resections in which a custom-made antibiotic impregnated cement mega-spacers during the first stage of a two-staged procedure for treatment of infection was implanted.

**Materials and Methods:** Between 2007 and 2010 10 cases with an infection at the site of a segmental tumor endoprosthesis were treated with a two-staged procedure; which includes placement of a custom-made antibiotic-impregnated cement mega-spacer after removal of the endoprosthesis and thorough debridement, followed by a course of intravenous antibiotics and delayed second-stage endoprosthesis reconstruction. Mega-spacers were prepared using "rapid prototyping" technology, metal-reinforced intramedullary femoral and tibial stems and increased constriction devices.

**Results:** There were 8 females and 2 males; the mean age of the patients was 59 (range 16-75). The spacers were implanted for a period of 15 weeks (range 12-20). The infection was controlled in all cases, and all the patients had an endoprosthesis reconstruction. No spacer cracks or dislocations were recorded during the study period. The antibiotics used were: vancomycin and gentamicin in 9 cases and vancomycin, gentamicin and clindamycin in the remaining case. The anatomic locations for the mega-spacers were 9 distal femurs and one total femur.

**Conclusions:** Currently, relevant aspects regarding spacers are being discussed, many of them controversial: range of motion, cost, roughness, antibiotic release, fracture, dislocation, and need for additional orthotic equipment. Resorting to specific technology it has been possible to utilize large spacers in special cases.

M. Galli Serra, W. Parizza, C. Autorino (Buenos Aires, Argentina)

**Background:** Surgery is the primary treatment and the only curative loco-regional approach of localized resectable soft tissue sarcoma (STS) in elderly patients with no evidence of metastatic disease. The aim of the present study was to analyze a group of patients with age between 65 and 85 years old with STS localized at the thigh in which a complete resection of the muscular compartment was done without muscular or tendinous reconstruction. Functional evaluation was assessed.

**Material and Methods:** We retrospectively reviewed 20 patients with a mean age of 73 years (85-67) who had STS resection of the thigh. There were 11 females and 9 males. Incisional biopsy was done in all cases prior to definitive surgery. Patients were followed for an average of 40.8 months (6-101).

Wide resection of the thigh compartment was done in all cases according to the anatomic localization, in order to obtain negative margins, no muscular or tendinous reconstruction were done in the present series. All patients received postoperative radiotherapy (4500 – 6000 Cgy) according to our institutional protocol. Functional evaluation was done with the MSTS score and the “Up & Go” test at their latest follow up.

**Results:** Of the 20 STS, 11 were localized at the anterior compartment, 5 at the medial compartment and 4 at the posterior compartment of the thigh. Histology confirmed 12 liposarcomas, 3 leiomyosarcomas, 2 undifferentiated pleomorphic sarcoma, 2 synovial sarcomas and 1 fibrosarcomas. AJCS: IB 6 cases, IIB 13 cases, IVA 1 case. Although all resections achieve negative margins, and the margins obtained were classified as “wide”, one patients had a local recurrence (case 12). Six complications were registered. MSTS score: 25,7 (21-30). “Up & Go” test: 11 patients with free movement, 6 patients with independence and 3 patients with variable movement. 10 patients died (6 pulmonary metastasis, 1 liver metastasis and 3 other medical conditions).

**Conclusions:** STS of the thigh in the elderly treated by muscular compartment resections and postoperative radiotherapy without reconstruction seems to be a reasonable therapeutic approach, it has a good functional result with no limitations in daily living activities and effective disease control.

## ONCOVASCOLARE SURGERY: MULTIDISCIPLINARY APPROACH IN THE REMOVAL OF THE MUSCULOSKELETAL TUMOR AND ASSOCIATED REVASCULARIZATION. RESULTS AND COMPLICATIONS.

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*Ippoliti A., Ascoli Marchetti A., Di Giulio L., Morelli M., Watchouang S.*

**Introduction:** The radical strategy of the tumor's removal associated with limb salvage has become a primary objective. The purpose of this study is to describe the characteristics and results of surgical options for patients with musculoskeletal cancer and indication for radical resection, in our recent experience in collaboration with the oncology center of Rome and the IFO Division of Orthopedics University of Rome Tor Vergata.

**Methods:** Between 2007 and 2011, were treated 30 patients affected by primitive and secondary musculoskeletal neoplasm with a mean age of 44 years (14-67 years) in 26 cases (86.6%) were required revascularization. Women accounted for 53.84% (14/26), 46.16% were men (12/26). The study included a preoperative biopsy of the lesion and ultrasonography and angio-CT with multiplanar reconstructions for the evaluation of the vascular anatomy.

**Results:** The average postoperative follow-up was 19.4 months. The reconstruction of the vessels has been implemented in 12/26 (46%) mainly using the autologous saphenous contralateral vein. The use of the prosthesis was performed in the others cases (with PTFE and Dacron K prosthesis). In 4 cases the patients had lower limb edema, with a distance venous patency of 80% and arterial patency of 100%. We had no mortality at 30 days. Two patients underwent VAC therapy. No amputations were performed at 30 days. In 14 patients was performed perioperative chemotherapy or radiotherapy. The data were analyzed using SPSS 18.0 for Windows.

**Conclusions:** A long-term evaluation is needed to determine the implications at a distance in patients undergoing radical resection of cancer in which are necessary for skills vascular surgery. The mortality gap is conditioned on the prognosis of neoplasm.

# FUNCTIONALIMPROVEMENTOFTHESHOULDERJOINTWITHAN INVERSE MEGA-PROSTHESIS FOR DEFECT RECONSTRUCTION AFTER PROXIMAL HUMERUS RESECTION

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A.Streitbuerger, H. Ahrens, G. Gosheger, M. Henrichs, J. Harges, W. Guder

Department of Orthopedics, University Hospital of Muenster, Münster, Germany

**Introduction:** The defect reconstruction of the proximal humerus with conventional tumour prosthesis after tumor resection results commonly in a disappointing functional outcome. The loss of the attachment of the rotator cuff and especially the loss of the axillary nerve restrict the active shoulder function severely. However, as experience in revision shoulder arthroplasty provide in patients with an intact deltoid function an inverse prosthesis improves the active range of motion in the shoulder joint significantly, even if the function of the rotator cuff is seriously limited. In the presented study we investigated if the use of an inverse prosthesis is able to improve active shoulder function after segment resection of the proximal humerus.

**Material/Methods:** We present the short and midterm results of 13 patients treated with an inverse tumour prosthesis for the reconstruction of the proximal humerus after resection of benign (1 giant cell tumour) and malignant bone tumours (6 primary bone sarcoma, 1 multiple myeloma, 5 carcinoma). Mean age at operation was 54 years. The mean postoperative follow-up was 25 months (range 4-95).

**Results:** Resection margins were wide in 8, marginal in 2 and intralesional in 1 patient. Mean reconstruction length was 12 cm (range 5-20). Mean operation time was 192 minutes. The axillary nerve was preserved in 76% (n=10). At latest follow-up the patients presented a medium MSTS-score of 24,1/30. The mean active arm abduction in the shoulder joint was 68° and 57° active arm elevation for all patients but significantly reduced for the 3 patients without deltoid function. 2 patients needed a surgical revision (1 prostheses removal because of deep infection and 1 revision because of joint instability).

**Conclusion:** The inverse prosthesis offers a significant improvement of active shoulder function in patients in which the axillary nerve can be preserved, compared to conventional proximal humerus endoprosthesis. For patients without deltoid function there is no benefit regarding to the active range of motion.

# TOTAL HUMERAL REPLACEMENT FOR SARCOMA. CONSIDERATIONS ABOUT 3 CASES.

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Delépine G<sup>1</sup>, Delépine F<sup>2</sup>, Markowska B.<sup>1</sup>

<sup>1</sup>Oncologic pediatric unit Raymond Poincaré Hospital Garches France

<sup>2</sup>Clinique du parc impérial 28 boulevard du tzarevitch 06045 Nice France

**Objectives:** With effective chemotherapy the gold standard for limb salvage is wide resection. Consecutively primary total humeral resection is nowadays rarely indicated. Three cases, one with very long follow up permit us to consider the aspects of reconstruction.

## **Materials:**

Case 1 A 35 year old man consult us for pain in the left arm. Ct showed a tumour invading the whole humerus. Open biopsy confirms a low grade fibrosarcoma. Total humeral resection was performed with an allograft replacement.

Years later a sub capital fracture of the humerus compelled us to put an proximal humeral prosthesis. 12 years later the resorption of distal allograft compelled us to insert an elbow hinge prosthesis.

25 years after resection patient in first remission is cured. According to Enneking's score function is rated good (patient works as police officer).

Case 2 January 2010 a boy of 17 come for a pathological fracture of the proximal part of right humerus. Without biopsy he is treated by nailing from the elbow. After 2 months the fracture healed but pain and bone swelling increased.

After 1 year an open biopsy is performed showing a telangectasic osteosarcoma.

As nailing disseminated the tumour throughout the diaphysis. extratumoral surgery necessitates total humerus resection. Replacement used a composite prosthesis with an upper humeral long stem prosthesis inserted in an wide elbow custom made prosthesis locked with a high dose Vancomycine loaded acrylic cement (8 grams of vancomycine in 80 grams of metacrylate).

Post operative dislocation of shoulder appeared compelling to re operate after completion of chemotherapy.

At last follow up the patient is in first remission. Esthetical aspect of limb is nice.

According to Enneking's score function is rated good

**Conclusions:** Despite the technical difficulties total humeral replacement give much better function than forequarter amputation of upper limb.

These observations plea for primary replacement by total humeral prosthesis rather than by allograft.

A constrained shoulder prosthesis seems useful

Adding high dose Vancomycine may help in decreasing the infection risk.



The main target is to implement principles of total tibia endoprosthesis by oncological patients in Russia. Nowadays there are only few events of total tibia endoprosthesis by oncological patients. We would like to introduce our own positive experience of total tibia endoprosthesis in Russia.

The female patient, aged 24, with diagnosis of Ewing's sarcoma is the right tibia. T2bN0M0, stage IIb. She has been ill since April, 2009. The first symptoms were: pain, lameness. The pain was getting harder, and with the lapse of time it stopped being removed with intake of nesteroidal anti-inflammatory medicines. The patient was executed a roentgenogram of the right tibia, according to its results a malignant shaft formation of the right tibia was suspected. To make the diagnosis more exact, the patient was delivered to us. Trepanobiopsy was carried out. In accordance with the results of a histological and immunohistochemical conclusion, Ewing's sarcoma was diagnosed. Chemotherapy by the scheme VIDE was started. Eight courses were held without any visual effect. It was decided to hold a course of radiotherapy, total radiation dose 40 gray and a course of chemotherapy by the scheme Vincristin 2 mg intravenously 1 time per week in duration of 1-3 weeks, cyclophosphan 400 mg intravenously 1 time per week in duration of 1-3 weeks. The 10<sup>th</sup> course of chemotherapy by the scheme VIDE was held.

It was intraoperatively identified involvement in the tumor process m. flexor posterior, m. flexor digitorum longus, flex hallucis longus. Resection of m. flexor digitorum longus, flex hallucis longus was executed on the level of the lower third of shank within intact tissues. The neurovascular bundle was saved. The bone defect was removed with the help of a module endoprosthesis Mutars (Implantcast, Germany). The knee joint was reconstructed with the help of M-O-M system. The ankle joint was reconstructed with the help of the original construction. Arthrodesis of ankle and heel bones was done with the help of a distal leg of endoprosthesis. A femoral leg and a leg of the ankle joint were fixed with bone cement. The body of endoprosthesis is clothed with a cover "Trevira". Endoprosthesis was sheltered with removed m. gastrocnemius caput medialis. Histological and immunohistochemical conclusions of surgical material showed a good response to executed treatment – the 3<sup>rd</sup> stage of medical pathomorphosis. Post-operative treatment was concluded in immobilization of the extremity with a brace by means of fixation of knee and ankle joints, using means of additional support. The wound healed up after primary tension. Roentgenograms showed stable fixation of endoprosthesis' legs. At this moment the patient is observed the 6th month after the surgical operation, adjuvant chemotherapy is held. The mark according to MSTs is 76% (23/30 possible points). Motion in the knee joint is 85 degrees, in the ankle joint is 25 degrees.

**Conclusions:** Taking into account a positive result of the first in East European Sarcoma Group total tibia endoprosthesis and a good functional result and social rehabilitation, it is possible to recommend this kind of complicated prosthesis in specialized centers by oncological patients after a thorough choice of patients.

## LONG TERM FOLLOW UP OF ACRYLIC RECONSTRUCTION AFTER RESECTION OF ILIAC SARCOMA OF ZONES 1,3 OR 4

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Delépine G., Delépine N., Alkhalaff S., Markovska B.

Oncologic pediatric unit Raymond Poincaré Hospital Garches France

**Objectives:** Location on iliac bone account for 20% to 30% of sarcoma.. Gold standard of local treatment is wide resection but till now few papers have tried to evaluate the long term results of reconstructive procedures when chemotherapy and /or radiotherapy are used.

**Materials and method:** 45 patients (26 males and 19 females aged 9 to 66 years) with bone sarcoma of innominate bone in Zone 1, 3 or 4 (without involvement of acetabulum) were treated and/or followed up by the same team in 24 years.. Histology was: chondrosarcoma (28), Ewing (14), osteosarcoma (2), MH (1)

Preoperative screening of patients included standard X rays, CT and bone technetium scan in all cases and MRI in 16 cases. Diagnosis was made by open biopsy except for 4 cases of chondrosarcoma for these preoperative screening was sufficient (and diagnosis confirmed by postoperative histological examination).

Following limb salvage using reconstruction of pelvis was performed with methyl metacrylate without hip prosthesis. Titanium screws were inserted in remaining bone before moulding of acrylic cement (2 to 3 packs of antibiotic loaded cement).

**Results:** With a median follow-up of 16 years (minimal 2-maximal 23.5) 12 patients died from disease after local recurrence (6) and / or metastases (8). One disease free survivor has been lost for follow after 3 years. The 32 others are disease free survivors.

**Prognostic value:** in our patients the prognosis was directly correlated with the histological grading (low grade chondrosarcoma have a 85% DFS) and in high grade tumours with the efficacy of the chemotherapy. For primary metastatic patients, when chemotherapy is suboptimal or margins contaminated , the prognosis is dismal. With our most effective protocols and free margins, metastatic lesions did not affect the disease free survival of our patients. Orthopaedic results : weight bearing was immediate in all cases. We observed 3 deep infections (2 compelled to make ablation of the cement) and 3 late mobilisations of cement.

In all other patients, the reconstructive procedure gave a good and stable functional result even in very long follow up.

**Conclusions:** Acrylic reconstruction is an easy and reliable reconstructive procedure after en bloc resection of iliac bone for malignant tumours in zone 1, 3 or 4. It is more reliable than bone graft when chemotherapy or radiotherapy are necessary.

# RECONSTRUCTION OF BONE DEFECTS FOLLOWING BONE TUMOR RESECTION WITH SEGMENTAL BONE TRANSPORT USING ILIZAROV CIRCULAR EXTERNAL FIXATOR

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*Bahtiyar DEMIRALP, Assoc.Prof. , Orthopaedics and Traumatology Department, Gülhane Military Medical Academy 06018 Etlik ANKARA TURKEY, Tel: +903123045513, e mail: bahtidemiralp@yhoo.com*

*Yüksel YURTTAS, Assistant Prof., Orthopaedics and Traumatology Department, Gülhane Military Medical Academy 06018 Etlik ANKARA TURKEY, Tel: +903123045534, e mail: yukselmd@yahoo.com*

*Ozkan KOSE, Specialist,. Orthopaedics and Traumatology Department, Antalya Education and Research Hospital, ANTALYA TURKEY, Tel: +905326422612, e mail: drozkankose@hotmail.com*

*Cemil YILDIZ, Prof., Orthopaedics and Traumatology Department, Gülhane Military Medical Academy 06018 Etlik ANKARA TURKEY, Tel: +903123045531, email: cyorto@yahoo.com*

*Mustafa BASBOZKURT, Prof., Orthopaedics and Traumatology Department, Gülhane Military Medical Academy 06018 Etlik ANKARA TURKEY, Tel: +903123045501, e mail: mbasbozkurt@ttnet.net.tr*

**Objective:** The purpose of this retrospective study is to report the long-term follow-up experience in the reconstruction of bony defects by Ilizarov's distraction osteogenesis using bone transport method following en bloc resection of bone tumors.

**Materials and methods:** En bloc resection was performed 11 patients with bone tumors between October 1991-December 2004 in our clinic. The mean age of the patients was 18 years (range, 7-42 years). Histological diagnosis was osteosarcoma in four cases, Ewing sarcoma in three cases, aggressive giant cell tumor in one, osteofibrous dysplasia in one, chondrosarcoma in one and osteoblastoma in one case. Either femur or tibia was involved in all cases.

**Results:** The average follow-up period was 101 months (range, 86-196 months) and bone defect after resection was 13 cm (range, 8-24 cm). The function of the affected leg was excellent in six patients, good in four and poor in one patient according to the modified system of the MSTs. One Osteosarcoma case died six year after the surgery. In two patients additional plate fixation had to be performed due to non-union at the docking site. Conclusion: Bone transport is biological reconstruction technique. In patients with long life expectancies, reconstruction with distraction osteogenesis seems to be an efficient method in the long-term follow up. However, long external fixation time is a disadvantage of this technique. Problems in patient compliance and possible complications such as nonunion should be promptly managed.

## SCAPULAR RECONSTRUCTIONS FOLLOWING RESECTIONS FOR BONE SARCOMA: RIZZOLI EXPERIENCE

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*Dr. Massimiliano De Paolis, Dr. Alessio Biazzo, Dr. Nicola Fabbri, Prof. P. Ruggirei*

*Istituto Ortopedico Rizzoli di Bologna, Italy.*

**Objectives:** Traditionally, sarcomas arising from the scapula have been treated with partial or total scapulectomy. Resection of the total scapula or the glenoid results in major functional disability. The goal after these resections is to restore shoulder girdle stability and preserve a normal function of the elbow and the hand.

We report our experience about three patients who had scapular reconstructions after scapulectomy for bone sarcoma.

**Materials and Methods:** From 2007 to 2010, three patients (all females), affected by low grade central chondrosarcoma (Stage IA) of the scapula, were treated with a scapular resection. The ages of the patients were 31 years, 59 and 69 years. The skeletal resections were classified according to the system of Musculoskeletal Tumor Society. Glenoid resection (S1) was done in two patients and total scapulectomy in one (S1-S2). Massive osteoarticular allograft was implanted in two cases (partial and total scapulectomy) and custom made prostheses in one (partial scapulectomy). The scapular allograft was fixed with plates and screws. The custom-made prosthesis was fixed to the residual scapula with screws. The acromion-clavicular joint was fixed with K. wire and artificial ligament in 2 cases, 1 screw in one. The joint capsule, tendon and the periscapular muscles detached, during the resection procedure, were reattached to their origins or sutured to their corresponding stumps of the allograft. Minimum follow-up was 2 years (range 2-5 years). Musculoskeletal Tumor Society (MSTS) and Constant score to evaluate the functional result, at latest follow-up, were used.

**Results:** Shoulder dislocation, aseptic loosening of the prostheses, infection, nonunions or fractures of the allograft was not noted during this period. The MSTS score was 80-86%, and the Constant score was 56-61%. All patients had a stable, cosmetic, painless shoulder and functional elbow and hand.

**Conclusion:** Scapular reconstruction with allograft or prostheses after tumor resection is safe procedure. Selected patients and accurate surgical technique were crucial to obtain good outcome.

Yang-Guk Chung, Yong-Koo Kang, Won-Jong Bahk, An-Hi Lee\*, Jung-Mi Park\*\*Hae-Kyoo Lee\*\*

Department of Orthopedic Surgery, Clinical Pathology\*, Radiology\*\*, College of Medicine, The Catholic University of Korea, Seoul, Korea

**Objectives:** Preoperative embolization in hypervascular metastatic or primary tumors may reduce the intraoperative hemorrhage and transfusion, which will facilitate the tumor resection and reconstruction. We evaluated the effect of preoperative embolization in hypervascular tumors.

**Materials and methods:** Since April, 2007, we performed preoperative embolization and tumor resection in 10 hypervascular metastatic or primary tumors.

Amount of intra-operative bleeding and transfusion and operation time were evaluated. There were 5 men and 5 women. Mean age was 54.5 years. Primary tumors were renal cell ca in 4, hepatocellular ca in 3, and aneurismal bone cyst, anaplastic thyroid ca and MPNST in one respectively. The locations of lesions were pelvis in 4, proximal humerus in 2, proximal femur in 2. Other rare sites were scapula and spine. Wide resections were performed in 3 and curettage and cementations with internal fixation in 7. The mean number of vessel embolized was 3.88.

**Result:** The average intra-operative blood loss was 1467 ml, ranged from 600 ml to 2500 ml. The average transfusion amount was 1003 ml, ranged from 350 ml to 2290 ml. The operation time ranged from 60 to 235 minutes.

All ten patients were hemodynamically stable during tumor resection or curettage. There was no embolization related complication.

**Conclusion:** Preoperative embolization and tumor resection and/or reconstruction facilitated the safe surgical treatment even in hypervascular metastatic or primary tumors.

## BONE ONGROWTH ONTO THE COLLARS OF SILVER COATED ENDOPROSTHESES. AN IN VIVO STUDY.

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FENTON, P. KOTECHA, A. WAFA, H. ABUDU, A. CARTER, S. GRIMER, R. TILLMAN, R. JEYS, L.

BONE TUMOUR UNIT, ROYAL ORTHOPAEDIC HOSPITAL - BIRMINGHAM, UK

Endoprotheses have expanded the limb salvage options in surgery for bone tumours, however infection remains a significant concern. Silver has well recognised antimicrobial properties. Recently there has been interest in the use of silver coated orthopaedic implants as a means of reducing infection. However the possible cytotoxic effects of silver ions on osteoblasts have potential implications for osteointegration of uncemented implants. The purpose of this study was to assess the bone ongrowth onto silver coated endoprotheses compared with implants without silver coating.

From a prospective bone tumour database we identified 31 patients who had silver coated primary endoprotheses implanted since 2005. Six patients were excluded due to inadequate follow up. In addition we identified 26 patients who had routine primary endoprotheses implanted over the same time period. There was no statistically significant difference in age, sex, or length of follow up between the 2 groups. Radiographs were reviewed for all patients and the ongrowth of bone onto the collar of the prosthesis was assessed as present or absent. The presence of bone ongrowth was compared between the 2 groups.

In the silver coated group the mean age was 36.3 years and mean follow up 19.4 months. In this group 7 out of 25 patients had radiographic evidence of bone ongrowth. In the non-silver coated group the mean age was 39.5 and the mean follow up was 17.3 months. Sixteen out of 26 patients had evidence of bone ongrowth. There was a statistically significant difference in the presence of bone ongrowth between the 2 groups ( $p=0.016$ , fisher exact).

This is the first in vivo study to assess bone ongrowth with silver coated prostheses that we are aware of. Our results suggest that ongrowth is reduced with silver coated endoprotheses. This could lead to increased rates of aseptic loosening with these implants.

Sharon Cardoni S.W. M.A.

National Unit of Orthopedic Oncology,

Tel-Aviv Sourasky Medical Center, Tel Aviv Israel

**Background:** The World Health Organization defines palliative care as a therapeutic approach for improving the quality of life of the patient and his family from the moment an illness is diagnosed and throughout its various stages. A global trend is developing that sees positive thoughts as a therapeutic element in general, and in incurable illnesses, such as osteosarcoma, in particular. Nevertheless, there are studies and evidence from patients that raise questions regarding this therapeutic approach and even note a possible, and perhaps destructive, negative impact.

**Coping with crisis:** The concept due to illness emphasizes the way in which the individual perceives his condition and ability to successfully handle it. Success has several implications in this process:

- To infuse the patients with hope and thus to help the illness
- The patient's ability to seek and find emotional support
- The ability to process medical information and to apply behaviors directed towards solving problems, while considering the changing reality

**The therapist's perception of the palliative treatment:** My hypothesis is that the encounter between the therapist and the patient that suffers from a life threaten disease, the palliative treatment is of clinical significance and impact on the patient's quality of life and his coping from both the dynamic and the practical aspects.

**Conclusions:** As part of the attempt to determine the correct approach to treating a life threaten illness, when viewing the patient within the anamnestic process, personality, social and environmental factors should be considered because they affect the patient's style of coping, and not to only assume that positive thought is the right path for him. Our key goal as therapists focuses on maintaining the quality of the patient's life within the framework of the existing conditions while considering two aspects – the medical and the emotional. The emphasis is on providing support, enhancing the means of coping, reducing the disparity between the existing resources and the resources needed, helping solve problems in diverse frameworks (community, hospice home base, and hospice), meeting requests in the current system, improving the immediate wellbeing and increasing the sense of control.

**Recommendations:** The change in the therapeutic approach should focus on positive thoughts and infusing hope as means of helping the patients and their families, rather than the therapeutic goal itself.

One should know how to make educated use that is suitable for the particular patient, and to find the balance between positive thoughts and infusing hope, and coping with the existing and the changing reality.



*Synnøve Granlien, Charlott Våde*

*OUS- The Norwegian Hospital*

*Oslo - Norway*

**Objective:** Increased attention on sarcomas for Health Care Professionals and if possible decrease time from appointment with G.P. or local hospital to right diagnosis and start of treatment.

Organize a meeting were sarcoma patients can meet and support each other.

**Materials and Methods:** Awareness day for health care professionals with lessons about what sarcoma is, how to detect, how to refer to sarcoma centers and how we treat sarcomas.

Gathering for sarcoma survivors and their relatives with teaching lessons, entertainment, food and beverages.

**Results:** 164 G.P's, Physiotherapists, Nurses and other Healthcare professionals participated at the Conference of Sarcoma Awareness.

250 Sarcoma Survivors and their relatives joined the evening event.

**Conclusions:** The response from the attendants shows that there is need for information and education about sarcomas for Healthcare professionals.

Former patients have responded that they need a fellowship to support and help each other during treatment and rehabilitation. We also started a Patient Association for sarcoma patients during the evening-event and by now have over 300 members.

*Antonietta Nardella,*

*IV clinica, Istituto Ortopedico Rizzoli. Bologna Italy*

The increasing of paediatric patients with orthopaedic oncologic pathology pushed us to: § Create a better facilities for both mother and child by creating dedicated rooms, spaces for game and study. § Directing the nurse's training to better care, skill in communications and apply new methodologies without using drugs in painful procedures. § Only for children dedicated spaces during the follow up visits, assuring the continuity of care with a dedicated medical doctor. The above improvement's actions have been realized during the last 4 years. Any differences of age among the patients in the same room during the hospitalization, as much as for the follow up was taken into account before of it. Thanks to the collaboration of all managers of the Institute and the sensibility to deal with the problem showed by both volunteers and benefactors, and the effort of the hospital care and medical staffs it has been possible to realize a better care and comfort facilities targeting the necessity of the paediatric patients with orthopaedic oncologic diseases.

## TAKING CARE ABOUT CHILDREN WITH CANCER AND THEIR SOCIAL ENVIRONMENT

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*Berthold S., Eisenreich B.*

*Department of Pediatric Oncology, Olgahospital Stuttgart, Germany*

Used to talk about highly specialized medical procedures and therapies, newest drugs, antibodies.... In the recent years more and more 'peripheral' issues gained our interest, like quality of life, prevention of long term side effects, family matters. In this spirit over the years many groups in pediatric oncology developed programs beyond primary medical care.

We would like to present a selection of these activities at our department, some of the projects older than 20 years. Quite popular is our summer camp 'Prima Klima' for children who have been touched with cancer or other chronic diseases. Characterizing and pivotal point is the staff: apart from some supporters all them recruit from former members of the camp, all of them having suffered from disease and therapy and sharing this experience with nowadays participants. This unique constellation will be one focus our presentation.

Accompanying activities take care about siblings, during therapy and afterwards, one project evaluates the influence of sports and physical activity during chemotherapy. With adults there is evidence of effective reduction of side effects and even risk for cancer relapse. Trying to establish a similar program for children hopefully we get comparable if not better results.

At last we want to allude briefly the care of another group of concerned people: ourselves! In the past we had a lot of psychological supervisions, but we discovered, that we achieved the biggest effect by becoming team-players. So we have a lot of collective activities like to go skiing, having summer and christmas parties, visiting Stuttgart's 'Oktoberfest'. These joint adventures help us to handle our straining work.

A poster presentation like this might be only a glimpse into these activities, but we hope we can convey an image how important they are for a comprehensive treatment of cancer.



**Progettazione&Realizzazione Evento:**



**Ad Arte Srl**

**Sede Legale:** Via M. D'Azeglio 51 - 40123 Bologna

**Sede Operativa:** Via G. Di Vittorio 2 - 40057 Cadriano di Granarolo E. (BO)

Tel. +39 051 19936160 • Fax +39 051 19936700

**[info@adarteventi.com](mailto:info@adarteventi.com) • [www.adarteventi.com](http://www.adarteventi.com)**